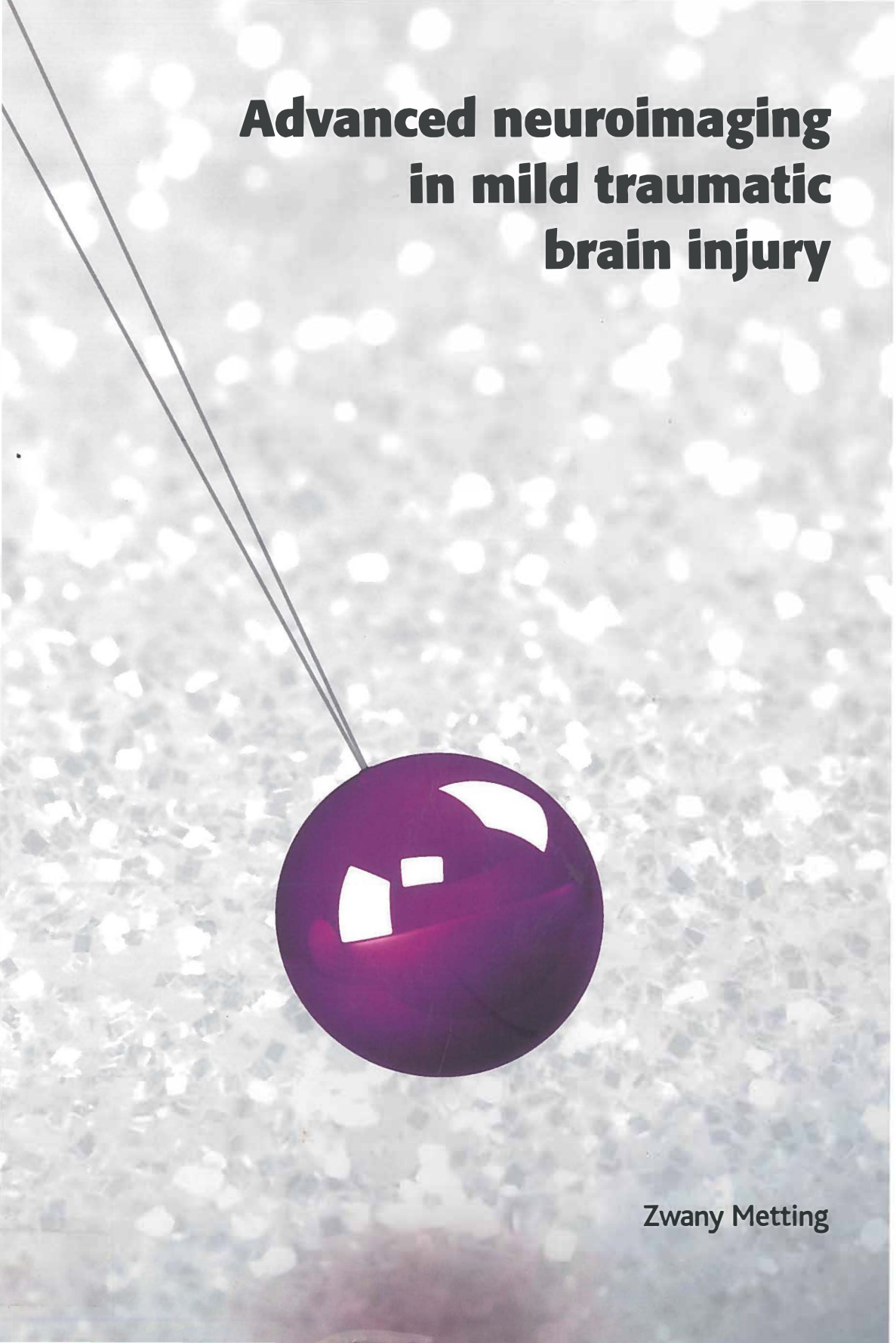
Advanced neuroimaging in mild traumatic brain injury



Zwany Metting

Advanced neuroimaging in mild traumatic brain injury

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Stellingen

behorende bij het proefschrift

Advanced neuroimaging in mild traumatic brain injury

Patiënten met licht traumatisch hersenletsel en een normale conventionele CT kunnen in de acute fase cerebrale perfusie stoornissen hebben welke van prognostisch belang zijn *(dit proefschrift)*

Posttraumatische amnesie is, hemodynamisch gezien, niet gecentreerd op één plek in het brein maar maakt onderdeel uit van een uitgebreider netwerk, waaronder de frontale grijze stof *(dit proefschrift)*

De relatie tussen cerebrale perfusie stoornissen in de acute fase van licht traumatisch hersenletsel en de lange termijn bevindingen, verkregen met diffusion tensor imaging en neuropsychologisch onderzoek, suggereert een pathofysiologisch continuüm *(dit proefschrift)*

Ook licht traumatisch hersenletsel kan stoornissen in de sociale cognitie tot gevolg hebben *(dit proefschrift)*

Een hogere frontale corticale bloed stroom bij vrouwen dan bij mannen geeft, in ieder geval, een kwantitatief verschil weer *(dit proefschrift)*

De wortels van de wetenschap krijgen lang niet de aandacht waarin de takken en vruchten zich mogen verheugen (Robbert Dijkgraaf)

People make rules to keep from making decisions

Het opvoeren van het stemvolume komt de communicatie met de-alles-behalve-slecht horende-mens niet ten goede

Een krent eet rozijnen in plaats van druiven

Binnen de perken zijn de mogelijkheden even onbeperkt als daarbuiten (Jules Deelder)

Zwany Metting, 11 februari 2013

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CONTENTS

Chapter

1

General introduction

MILD TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) is one of the most common neurologic disorders and a leading cause of death and disability. [1-3] In the Netherlands, the annual incidence of patients with TBI admitted to the hospital is approximately 113 per 100.000 inhabitants, [4] varying from 100-300 per 100.000 inhabitants depending on the population studied. [5-11] Population based surveys on self-reported mild TBI yield even much higher rates of more than 600 per 100.000 inhabitants. [7] The majority (80-90%) of patients is classified as mild TBI, defined by a Glasgow Coma Score (GCS) from 13 to 15 with at least a period with loss of consciousness or loss of memory for events. [8,9,12,13] Most of these patients recover within weeks to months without specific therapy. [14] However, a subgroup continues to experience disabling symptoms, like headaches, drowsiness, fatigue, irritability, poor concentration, sleep disturbance and memory dysfunction, interfering with return to work or resumption of social activities. [15-21] These symptoms not only cause a personal but also a socioeconomic burden, since most often if affects young patients in their twenties and thirties with full occupational status. [10] In Europe, TBI in general accounts for the largest number of total years lived with disability and ranks in to the top three of highest hospital costs per inhabitant. [22,23]

It is of paramount importance to identify those patients who are prone to develop cognitive disability to institute early rehabilitation to facilitate resumption of activities of daily living and return to work. [10,12]

For years, symptomatic mild TBI patients with persistent symptoms were suspected of exaggeration, even of malingering, but in the past few decades an increasing number of studies has revealed coherence between symptoms and changes on imaging studies in mild TBI, thus suggesting that real structural and physiological changes underlie at least part of the persistence of symptoms after mild TBI. [24-26]

PROGNOSTIC FACTORS

There is controversy in the literature regarding the additional prognostic factors in patients with mild TBI, especially when compared with the well-documented outcome in patients with moderate to severe TBI.[27,28] Patients often experience a combination of physical, emotional and cognitive symptoms.[29] One of the problems is the lack of a consistent definition of mild TBI.[19,30] A large cohort study of mild TBI patients revealed that, in addition to the presence of extracranial injuries, age was one of the strongest negative outcome predictors.[31] Also duration of posttraumatic amnesia (PTA) and complaints at 1 and 3 months after injury were found to be significant predictors for outcome.[19] A review of the literature by Carroll and colleagues summarised a variety of additional prognostic factors like sex, injury severity, IQ, psychological status and trauma mechanism.[14] Most studies regarding outcome in mild to moderate TBI relate persistent cognitive complaints to physical and structural features. The actual mechanism may be more complex as specific premorbid patient characteristics may also be relevant. Personality traits like coping strategy, illness perception and psychological status are likely to attribute to the outcome. In TBI patients it was consistently found that the use of active coping strategies relates to better outcome and functioning.[32-34]

THE ROLE OF CONVENTIONAL IMAGING

The first and most commonly used imaging technique in the acute phase of TBI is computed tomography (CT). CT is the most relevant imaging procedure for the detection of lesions eligible for surgical intervention, and it can be rapidly and easily performed, even in agitated patients.[35-37] In the total population of patients with mild TBI who obtained a CT scan, the incidence of abnormal findings is about 15%. This increases up to 50% when only in those patients with neurological symptoms a CT scan is performed.[38] However, a physical examination without focal neurological abnormalities does not rule out CT abnormalities.[39] The overall sensitivity of CT for the detection of abnormalities in acute head trauma is estimated at 63-75%.[40,41] The presence of intraparenchymal lesions, oedema[40] and the number of hemorrhagic contusions in particular[31] are of prognostic value in mild to moderate TBI. An important issue is that approximately 20% of the patients who sustained mild to moderate TBI with a normal CT on admission experience problems with resuming work,[40] suggesting that the conventional CT scan has limited ability to detect structural and functional abnormalities.

Magnetic resonance imaging (MRI) is the technique of choice in the subacute phase of TBI and during follow-up, although it is as reliable as CT in detecting hemorrhages in the acute phase.[35,42-44] Currently applied MRI modalities in TBI include T2*-weighted gradient-recalled-echo (GRE) sequences and susceptibility-weighted imaging (SWI), and are superior to T1, T2-

weighted spin echo (SE) and fluid attenuated inversion recovery (FLAIR) sequences in the detection of hemosiderin deposits. Applying these various modalities, MRI is more sensitive than CT in detecting diffuse axonal injury (DAI) and non-hemorrhagic contusions,[41,45,46] especially in the frontal and temporal regions at the base of the skull.[40,47] In addition, small subdural hematomas and brain stem injury are more easily detected.[48] Interestingly, in one in four patients good recovery is seen despite the presence of lesions on MRI scanning.[49] On the other hand, approximately 15% of the patients with a normal MRI have a suboptimal outcome and problems with resumption of work.[40] Due to these inconsistencies with regard to the relation between the presence of lesions and outcome, one has to consider whether appropriate imaging sequences are applied.[50] The prognostic relevance of T2*-weighted GRE and SWI has to be elucidated in more detail as the few available studies do not reveal uniform results.[51,54]

Advances in neuroimaging techniques may improve insights in the pathophysiological mechanism of mild TBI, increase the sensitivity for detecting abnormalities, allow the development of better prognostic indicators and, hence, help facilitating early institution of rehabilitation in order to improve outcome.

THIS THESIS

Aim

The goal of this thesis was to provide more insight in the pathophysiological mechanisms underlying mild TBI with advanced neuroimaging methods in order to obtain better prognostic indicators. Therefore, our research has focused the prognostic value of perfusion CT imaging in the acute phase of mild TBI. Additionally, the relation of acute perfusion CT imaging with neuropsychological testing and diffuse tensor imaging (DTI) during follow-up was assessed.

Methods

Patient population

Patients eligible for this study were prospectively identified for enrolment and had to fulfill the following inclusion criteria: (1) age 18 to 65 years; (2) mild TBI defined as an initial GCS from 13 to 15; (3) posttraumatic amnesia (PTA) and (4) inclusion within 12 hours after injury. Patients with a history of neurological or psychiatric disease, mental retardation, addiction to alcohol or drugs or inability for long-term follow-up were excluded. Pregnancy, history of diabetes, nephropathy and contrast allergy were additional exclusion criteria.

On admission

After arrival at the emergency department, the GCS (Appendix I) and duration of PTA were determined by the attending neurologist as a part of the neurological examination. At the emergency department an intravenous line was inserted and blood was sampled for renal function and biomarker analysis. Thereafter, a conventional non-contrast CT and a perfusion CT were performed. If the patient still was in PTA when admitted to the ward, registration of PTA (Appendix II) was started by the nursing staff.

Follow-up

During follow-up neuropsychological testing and MRI-scanning, including DTI sequences, were performed in a subgroup of patients. Outcome of the whole patient group was assessed by a neurologist (J.v.d.N.), who was unaware of perfusion CT results at six months after injury in our outpatient clinic according to the extended Glasgow Outcome Scale (GOSE, Appendix III) [55] and return to work (RTW, Appendix III).

Outline of this thesis

A review on neuroimaging in mild to moderate TBI is described in **chapter 2**. It covers the advantages and limitations of various techniques regarding the initial assessment and identification of brain abnormalities and their role in the prediction of outcome. In **chapter 3**, acute cerebral perfusion CT measurements in mild TBI patients are described and compared

with healthy control subjects. In addition, the prognostic value of perfusion CT imaging in relation to outcome as defined by the GOSE and RTW is examined. The differences in cerebral perfusion between patients scanned during or after their episode of PTA is outlined in **chapter 4**. Assessing the outcome prediction of the biomarkers Glial Fibrillary Acid Protein (GFAP) and S100B is described in **chapter 5**, which also details on the relation with non-contrast CT and MRI. DTI findings during follow-up after mild TBI is outlined in **chapter 6** and is compared to perfusion CT findings in the acute phase of injury. Next, the relation with acute perfusion CT imaging and neuropsychological testing during follow-up is discussed in **chapter 7**, focusing on the role of the frontal and parieto-temporal cortex. Finally, in **chapter 8** a summary of the results is given as well as an integrated general discussion of the postulated pathophysiologic mechanisms of mild TBI and the role of neuroimaging in these processes. The prognostic value of imaging is discussed, closing with future perspectives.

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Chapter

2

Structural and functional neuroimaging in mild to moderate traumatic brain injury

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ABSTRACT

Traumatic brain injury (TBI) is a major cause of disability and death in adults. Significant developments in imaging techniques have contributed to the knowledge of the pathophysiology of TBI. Although extensive research is available on severe TBI, less is known about mild to moderate TBI despite the fact that the most patients sustain this type of injury.

In this review, we focus on structural and functional imaging techniques in patients with mild to moderate TBI. We discuss conventional computed tomography (CT) and magnetic resonance imaging (MRI), including different MRI sequences. With regard to functional imaging, single photon emission computed tomography (SPECT), perfusion-weighted MRI, perfusion CT, positron emission tomography (PET), magnetic resonance spectroscopy (MRS), functional MRI (fMRI) and magnetoencephalography (MEG) are discussed. Advantages and limitations of these various techniques are addressed with regard to the initial assessment and identification of brain abnormalities and their role in the prediction of outcome.

INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of disability and death in adults, and most patients (85-95%) are classified as having mild to moderate TBI. [1-5] Most of these patients recover within weeks to months without specific therapy. However, a subgroup continues to experience disabling symptoms that interfere with their return to work or resumption of social activities. [6-10] The burden of these symptoms is not only personal but also socioeconomic, as they common in young patients in their twenties and thirties with full occupational status. It is of paramount importance to identify those patients who are prone to develop cognitive disability to promote early rehabilitation. [11-13]

In recent decades major advances in the development of imaging techniques have contributed to the knowledge of the pathophysiology of TBI. The capibilities of structural imaging techniques have been expanded by various techniques suitable for visualizing hemodynamic and metabolic changes in the brain. Concurrently, the treatment of trauma patients is increasingly guided by the rapid assessment of primary damage and prevention of further deterioration. Hence, selection of the technique most valuable in guiding management during the acute phase of injury is essential, as is the assessment of the additional value of the technique in predicting outcome.

In this article, we present an overview of the current imaging techniques in terms of their ability to reveal structural or functional brain abnormalities in patients with TBI. We focus on patients with mild to moderate TBI, defined by a Glasgow Coma Score (GCS) of more than 8, as the majority of patients sustain this type of head injury and, in contrast to severe TBI, scarce information is available on this topic. As some extensive reviews of imaging studies in children are already available, this review focuses on studies of mild to moderate TBI in adults. [14-16] We discuss advantages and limitations of various techniques are addressed with regard to the initial assessment and identification of brain abnormalities and their role in the prediction of outcome.

STRUCTURAL IMAGING

In TBI, the mechanism of damage can be classified as primary and secondary injury. In general, structural imaging techniques are used to visualise primary brain injury.

Primary brain injury occurs at the moment of impact, with diffuse axonal injury (DAI) being the most important primary lesion. [5,17-19] DAI is a consistent finding in mild, moderate and severe TBI, although the severity increases with that of the brain injury. [20-22] Primary brain injury also comprises focal abnormalities, such as contusions and hematomas, as a result of either direct external contact forces or from the movement of the brain within the skull. [17,23] Secondary brain injury, on the other hand, develops within hours after impact as a result of primary injury and

mainly consists of ischemia, [24-26] that is best visualised using functional imaging. In the emergency setting, clinical management is guided by the imaging of structural abnormalities requiring acute interventions. During follow-up, structural imaging techniques are most commonly used to explain postconcussional symptoms or to predict outcome. Structural imaging techniques in patients include computed tomography and magnetic resonance imaging.

Computed tomography

Computed tomography (CT) is one of the first developed and most commonly applied imaging techniques in the acute phase of TBI and can be used to detect hemorrhage, parenchymal injury and skull fractures. CT is the most relevant imaging procedure for the detection of lesions eligible for surgical intervention, as it is rapidly and easily performed, even in agitated patients. [17,27,28] For mild and moderate TBI, there is no agreement about routine CT scanning. There is a substantial variation among institutions in the ordering of CT for patients with mild TBI, ranging from 16 to 74%. [29] When all patients with mild to moderate TBI are scanned, the incidence of abnormal findings is about 15%, increasing to 50% when a CT scan is done in only those patients with neurological symptoms. [30] However, absence of focal neurological abnormalities on physical examination does not rule out CT abnormalities. [31] Since the introduction of the National Institute for Health and Clinical Excellence (NICE) guidelines [32] for management of TBI, the use of CT has substantially increased, [33,34] with the reported incidence of intracranial abnormalities of approximately 10%. A low Glasgow Coma Score (GCS), the presence of a skull fracture, old age, and focal neurological signs are associated with a higher incidence of abnormal CT findings in patients with mild TBI. [35-37] The overall sensitivity of CT for the detection of abnormalities in acute head trauma is 63-75%. [38,39] In patients with mild to moderate TBI, oedema or lesions on CT are related to problems with resumption of work. [39] Also, the presence of subarachnoid blood on CT is a significant predictor of outcome. [40] Contusions in frontal and temporal lobes, when present on CT, result in relevant deficits in outcome caused by behavioural and cognitive problems. [41,42] Lesion size is inversely associated with outcome. [43] Furthermore, about 20% of patients who sustain mild to moderate TBI without abnormalities on the admission CT have problems with resuming work, [39] suggesting that the conventional CT scan has limited ability in detecting structural and, as least as important, functional abnormalities.

Magnetic resonance imaging

T1, T2, FLAIR and T2-weighted gradient-recalled-echo*

Magnetic resonance imaging (MRI) is the technique of choice in the subacute phase of TBI and during follow-up. The difficulty of using MRI to evaluate skull fractures, the limitations in monitoring patients during MRI, and the susceptibility to motion artefacts related to the relatively long exposure time discourage the use of this technique in the acute phase of TBI. Although in earlier studies MRI was inferior to CT in the detecting parenchymal and subarachnoid

hemorrhages, MRI is now as reliable as CT in detecting these hemorrhages in the acute phase because of improvements in MRI imaging techniques. [17,44-46] Moreover, MRI is more sensitive than CT in detecting DAI and non-hemorrhagic contusions, [22,38,47] especially in the frontal and temporal regions at the base of the skull. [39,46] MRI is also more sensitive in detecting small subdural hematomas (Figure 1) and brainstem injury. [48] A third of patients with mild to moderate TBI have focal atrophy in the frontal and temporal regions on MRI in the chronic phase, which is predictive of outcome. [39] In addition to whole brain atrophy, the number, size and depth of lesions were also associated with the degree of unconsciousness and outcome. [39,49-51] Serial MRI scanning showed a resolution of lesions as well as simultaneous improvement of neuropsychological testing. [46,52]

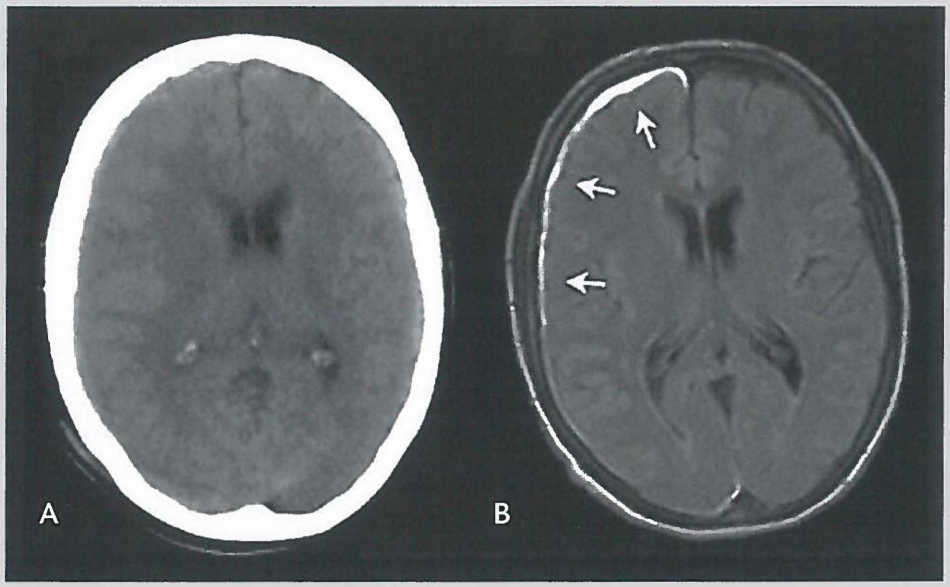

Figure 1. Subacute subdural hematoma.
A 33-year-old woman who was involved in a car accident. Her initial Glasgow Coma Score (GCS) was 11. Non-contrast computed tomography (CT) on admission showed a doubtful hyperdense ridge over the right frontal lobe (A). FLAIR-weighted magnetic resonance imaging (MRI) sequences on day 15 after trauma revealed a subdural hematoma in this area (B). Her clinical condition remained stable.

In one of four patients good recovery is observed despite the presence of lesions in MRI scanning. [53] However, about 15% of the patients with a normal MRI have a suboptimal outcome and problems with resumption of work. [39] Because there are some inconsistencies about lesions and

outcome, consideration of whether the appropriate imaging sequences have been selected is important.

For years, T1 and T2-weighted spin echo (SE) and fluid attenuated inversion recovery (FLAIR)-weighted sequences were the most commonly used MRI sequences in TBI. T2-weighted SE sequences seem to be more sensitive in detecting contusions compared with T1-weighted SE sequences. The sensitivity of FLAIR-weighted sequences is the same as or better than T2-weighted SE sequences in the assessment of traumatic lesions. [54] In the acute stage, FLAIR-weighted sequences are used for the detection of DAI, oedema and hemorrhage whereas in the subacute and chronic stages FLAIR-weighted sequences are mainly used for the detection of gliosis. [27] Although about 80% of DAI lesions were thought to be non-hemorrhagic in nature, improved MRI techniques indicate that the proportion of hemorrhagic DAI lesions is in fact much greater than previously thought. T2*-weighted gradient-recalled-echo (GRE) sequences enable visualisation of hemosiderin deposits as a result of hemorrhage, possibly as a result of DAI. [55,56] T2*-weighted GRE imaging is better than T1-weighted and T2-weighted SE sequences in the detection of traumatic lesions (Figure 2). [56,57]

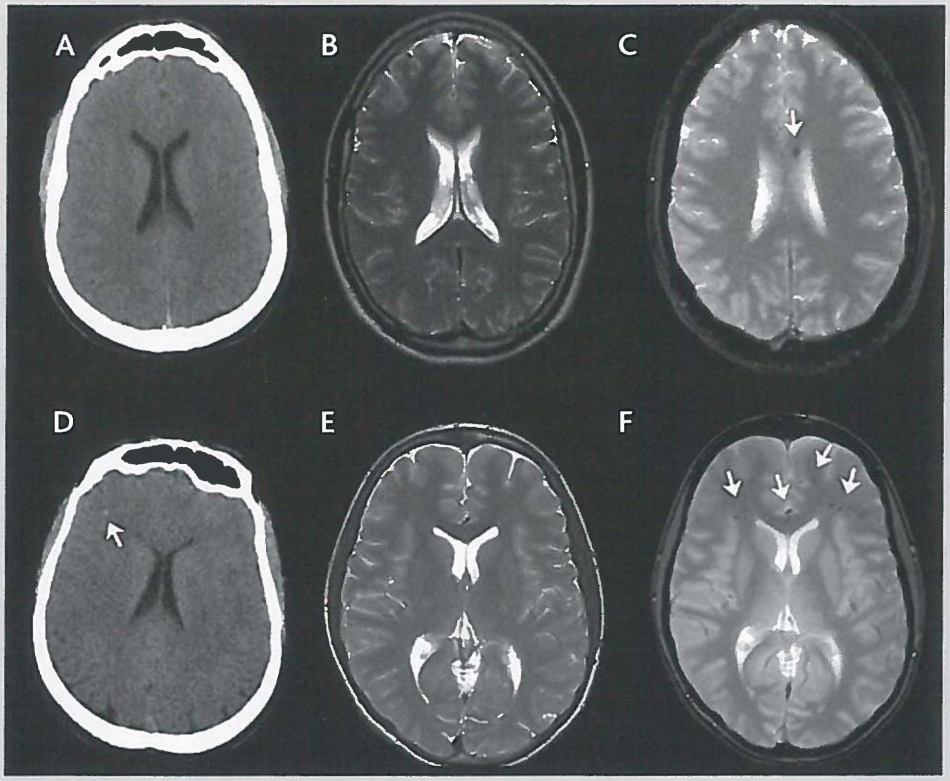

Figure 2. Diffuse axonal injury on magnetic resonance imaging (MRI) during follow-up.
Top: a 31-year-old man who was involved in motor cycle accident. His initial Glasgow Coma Score (GCS) was 13. Non-contrast computed tomography (CT) on admission showed no abnormalities (A). Magnetic resonance imaging (MRI) was obtained 6 weeks after trauma. MRI T2-weighted spin echo (SE) sequences revealed no obvious abnormalities (B) whereas T2*-weighted gradient-recalled echo (GRE) images showed a hypointense lesion in the corpus callosum suggestive of diffuse axonal injury (C).
Bottom: a 23-year-old woman after a bicycle accident. Her initial GCS was 12. Non-contrast CT on admission showed one small hemorrhagic lesion in the right frontal lobe (D). MRI was obtained 7 weeks after trauma. T2-weighted SE sequences (E) revealed no lesions while T2*-weighted GRE sequences (F) revealed multiple hypointense lesions in the frontal lobes extending into the corpus callosum, suggestive of diffuse axonal injury.

In a study of patients with TBI of varying severity, the number of lesions on T2*-weighted GRE sequences were positively correlated with outcome, whereas on T2-weighted SE it was not. [56] In patients with mild TBI, there is a relation between MRI abnormalities detected within 72 hours of injury and neuropsychological deficits. [58,59] However, there was no relation between these imaging findings and return to work or postconcussive symptoms, [58] although slower reaction times were detected. [60] Susceptibility-weighted imaging (SWI) is the most recently

developed MRI technique and has a high sensitivity for hemosiderin. [61] Although further research is needed, the sensitivity of SWI for the detection of hemorrhagic lesions in patients with TBI is probably higher than that of T2*-weighted GRE sequences (Figure 3). [62] In general, for the detection of posttraumatic abnormalities within one to three months after injury, MRI is preferred, on the condition that appropriate MRI imaging sequences are used. [63]

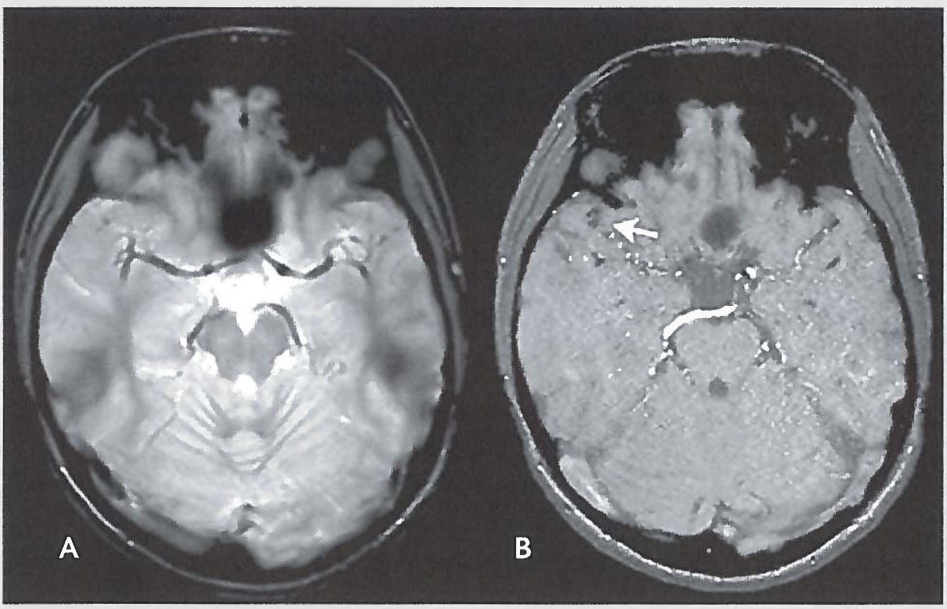

Figure 3. Susceptibility-weighted imaging (SWI).
Images of the second patient of Figure 2 after a bicycle accident. T2*-weighted gradient-recalled echo (GRE; A) revealed doubtful lesions in the temporal regions while these lesions were clearly visible on SWI (B).

Diffusion-weighted imaging

Diffusion-weighted imaging (DWI) is another MRI modality that is primarily used to detect vasogenic or cytotoxic oedema. This technique is sensitive to the random movement of water molecules and can distinguish between lesions with increased and restricted diffusion in patients with TBI. The apparent diffusion coefficient (ADC) can be calculated and used to quantify the degree of restriction of water molecules caused by TBI. DWI is widely used in cerebral ischemic stroke, showing changes in DWI before the onset of visible abnormalities seen in conventional imaging. [64,65] In a few studies comprising mild TBI, diffusion abnormalities were seen within days after injury. [59,66] In severe TBI, DWI can be used to identify DAI as hyperintense lesions that are not visible on T2-weighted SE, T2*-weighted GRE or FLAIR-sequences. Most of these DAI lesions

show decreased diffusion probably due to cytotoxic oedema within days [67] to weeks after injury. [68,69] Although cytotoxic oedema predominates in TBI, there is high diffusion in the acute phase, probably due to vasogenic oedema. [66,67] DWI is less sensitive than T2*-weighted GRE images for detecting hemorrhagic DAI lesions. [67] However, the volume of lesions depicted with DWI shows a stronger correlation with clinical outcome in patients with TBI than FLAIR, T2-weighted SE or T2*-weighted GRE sequences. [70]

Diffusion tensor imaging

A relatively new MRI technique, diffusion tensor imaging (DTI), is an extension of DWI that allows the reconstruction of white matter tracts in the central nervous system. [71-73] The advantage of DTI is that it can be used to visualise axonal injury, the major pathological substrate of TBI. This technique measures the degree and directionality of water diffusion. Water diffusion in tissue is modified by its structural environment, and in white matter, diffusion is greatest along fibre tracts parallel to the myelin sheaths. With DTI the mean diffusivity and fractional anisotropy can be determined; both parameters are a measures of axonal integrity. DTI allows the reconstruction of the diffusion direction, generating colour maps that reveal the location and orientation of major white matter fibre tracts in the central nervous system. [74,75] In patients with mild TBI, DTI in the acute phase showed reduced fractional anisotropy in the normal appearing white matter, predominantly in the internal capsule and corpus callosum, most likely as a consequence of DAI. [76] This pattern was also seen days to years after mild TBI. [77] Of interest here is that brains of asymptomatic professional boxers revealed comparable changes. [78] The degree of these water diffusion abnormalities is correlated with the acute GCS and the Rankin score at discharge. [72] Moreover, reduced fractional anisotropy in the splenium is related to cognitive dysfunction more than one year after injury. [79] Thus far, there have been inconsistent findings about diffusivity in TBI, probably related to differing pathophysiological processeses that are thought to evolve over time. [80] Restricted diffusivity was observed within the splenium and in the periphery of focal lesions, without any associated increase in T2-weighted signal intensity. [72,81] In chronic TBI survivors, however, there was a positive correlation between increased diffusivity in widespread areas of the cerebral cortex and learning and memory problems. [82] DTI provides a powerful non-invasive tool to study complex brain tissue architecture. With recent improvements in hardware, DTI acquisition and calculation times have been reduced to allow complete brain coverage and visualisation in colour maps of white matter tracts in a clinically acceptable period. More experience in DTI is needed, both for research and clinical applications.

In summary, structural imaging techniques, such as conventional CT and MRI, depict primary traumatic brain injury. The timing of imaging is important as information provided by CT imaging is most appropriate early in the course of injury and MRI methods are more helpful in the recovery phase. However, conventional CT and MRI have a limited negative predictive value, as the absence

of abnormalities is no guarantee of optimal outcome. The first results of MRI modalities based on diffusion methods such as DWI and DTI in TBI are promising. As diffusion-based methods indirectly rely on the energy status of the cells, these techniques could provide information on secondary injury. Further investigation is needed, especially in patients with mild to moderate TBI. Because conventional CT and MRI cannot show functional cerebral changes and therefore secondary brain injury, functional imaging techniques might be of more value in predicting outcome.

FUNCTIONAL IMAGING

Functional imaging techniques are used to measure hemodynamic or metabolic changes in the brain, mainly in the subacute phase of injury when secondary injury is developing. Secondary brain damage mainly consists of ischemia and is found to be present in more than 80% of fatal cases of TBI. [25] Even in monitored patients, ischemic damage occurs. In a series of patients with differing severity of TBI, 92% had one or more ischemic insults lasting for at least five minutes, despite being monitored in a well-equipped intensive care unit. [5] Functional imaging studies include hemodynamic imaging such as single photon emission computed tomography (SPECT) and positron emission tomography (PET), although the latter technique also provides information on the metabolic status of the brain. Although Xenon-CT was one of the first techniques used to examine perfusion in TBI patients, information is available mainly on severe TBI and as such is not relevant to this review. Imaging techniques such as perfusion MRI and perfusion CT are described, in which hemodynamic imaging is added to a modality originally used for structural imaging, thereby expanding the possibilities for the visualisation of brain abnormalities. Advanced MRI techniques such as functional MRI (fMRI) and magnetic resonance spectroscopy (MRS) provide information on the metabolic state of the brain with the former combining the accuracy of MRI with information on activation patterns of localised brain functions and the latter providing information on the metabolic state of the brain.

Single photon emission computed tomography

Single photon emission computed tomography (SPECT) is a procedure that provides an indirect indicator of brain metabolism by measuring cerebral blood flow (CBF). [83] Several radiotracers are available, with 99mTc-hexamethylpropyleneamine oxide (HMPAO) being the most common. [84] In 40-70% of patients with mild to moderate TBI, abnormal SPECT findings are observed, [60,83,85-88] especially within the first three months after injury. [85] Most of these patients have areas of hypoperfusion, predominantly located in frontal and temporal lobes, basal ganglia and thalami. Hypoperfusion seen on SPECT imaging correlates with the duration of posttraumatic

amnesia (PTA) after mild TBI (Figure 4). [89,90] Also, hypoperfusion on SPECT imaging is shown to be correlated with loss of consciousness and postconcussional syndrome. [90] In symptomatic patients with long-standing mild TBI and unremarkable structural brain imaging, reduced CBF is seen on SPECT imaging, concordant with neuropsychological testing. [91] A negative initial SPECT study is a reliable predictor of a favourable clinical outcome at three months after mild TBI. [53,87]

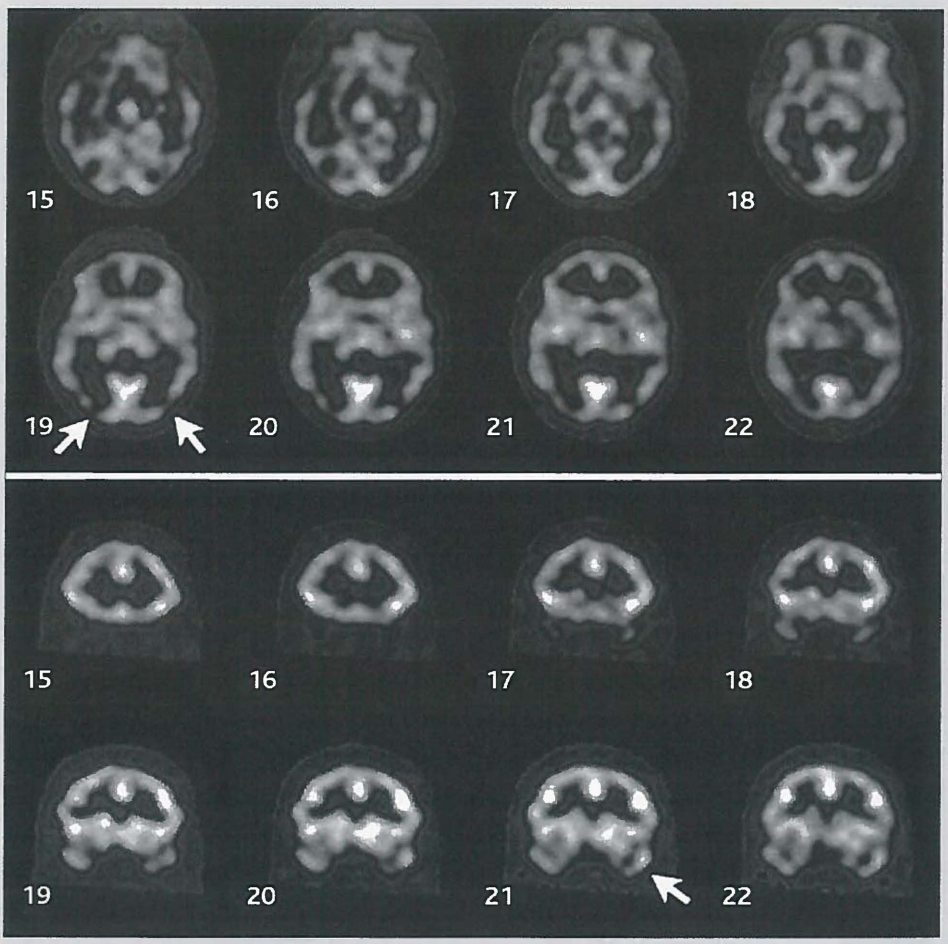

Figure 4. Single photon emission computed tomography (SPECT).
A 29-year-old woman with posttraumatic amnesia lasting 35 minutes. There is diminished perfusion in bilateral occipital and left temporal lobes.
(Published with permission of Dr. M. Lorberboym, originally published in Am J Emerg Med 2002;20:310-313).

In general, HMPAO SPECT seems to be more sensitive than CT or MRI in the detection of brain abnormalities in patients with mild to moderate TBI, with a larger area of involvement on SPECT than on CT. [92,93] However, the greater number of articles describing the use of SPECT in mild TBI than any other imaging modality does not indicate that it is more sensitive, because its application is still limited by its poor resolution, radiation exposure and difficulty in obtaining quantitative data. [94,95]

Perfusion-weighted MRI

Perfusion-weighted MRI, in which hemodynamically weighted MR sequences are based on the passage of a contrast agent through the brain, is sensitive to microscopic tissue-level changes in cerebral blood volume (CBV), and parameters like mean transit time (MTT) and CBF can be obtained. [96] Garnett and colleagues performed a perfusion MRI study in the subacute phase of TBI and found low CBV in regions of focal pathophysiology in patients with contusions and oedema visible on conventional MRI. In addition, there was one group of patients who had reduced CBV in a normal-appearing brain. These patients had a significantly worse clinical outcome than patients without abnormalities on perfusion MRI. Furthermore, these measurements were present on average ten days after the injury, implying that delayed changes in hemodynamic parameters, and not just acute changes, may be involved in determining clinical outcome. [64,97] An important limitation of this technique is that quantification remains difficult, together with limited application in the emergency setting. Furthermore, the use of a contrast agent is needed, unless the more recently developed spin-labelling technique is used.

Perfusion CT

Perfusion CT data are obtained by monitoring the first pass of an iodinated contrast agent bolus through the cerebral vasculature. Investigators can then calculate parameter maps of CBV, MTT and CBF (Figure 5), and the use of regions of interest allows quantification of the perfusion in the brain. [95,98-100] In recent years, the broad introduction of fast multi-detector CT systems and the development of commercially available software for perfusion analysis have facilitated the application of cerebral perfusion imaging in the clinical setting. [95]

After first being used in stroke patients, this technique is gradually being used in those with TBI. Perfusion CT features specific patterns in the acute phase related to outcome in patients with severe TBI. Normal brain perfusion or hyperemia is seen in patients with favourable outcome and oligemia is seen in patients with unfavourable outcome. Perfusion CT is more sensitive than conventional unenhanced CT in the detection of cerebral contusions, featured as areas with lowered CBF and CBV and increased MTT. [101] Also, in the first study of TBI in children and in patients with mild to moderate TBI, there were comparable abnormalities [102,103] Perfusion CT values of CBV were significantly lower in the immediate vicinity of epidural or subdural hematomas. [101] Apart from advantages, such as low exposure time and 24 hour availability in

most hospitals, use is limited by partial brain coverage and radiation exposure. [98,99] The promising potential of perfusion CT in the detection of secondary ischemic changes in the acute phase of brain injury is yet to be proven in mild to moderate TBI patients.

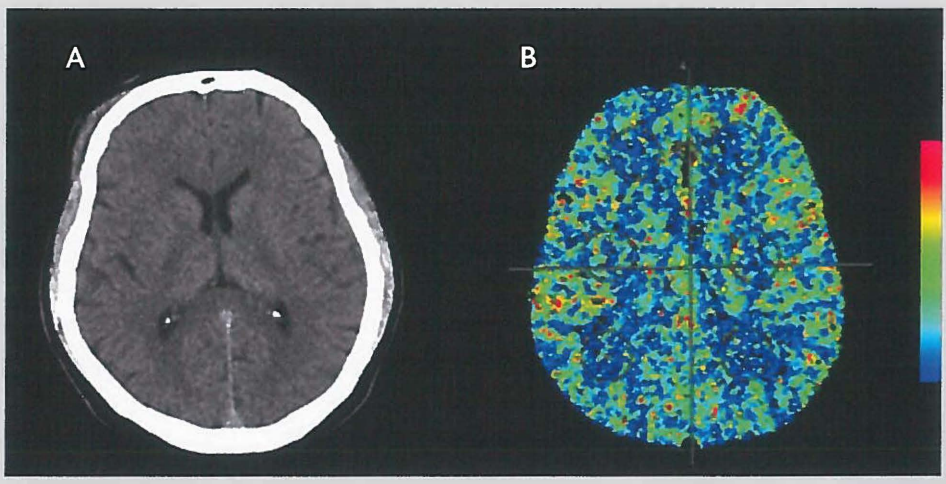

Figure 5. Perfusion CT.
A 49 year-old-man who was involved in a bicycle accident. His initial Glasgow Coma Score was 14. Non-contrast CT at admission showed no abnormalities (A) while the perfusion CT revealed hypoperfusion in the frontal and occipital lobes (B).

Positron emission tomography

Several studies have investigated the use of positron emission tomography (PET) for the evaluation of patients with TBI. PET provides tomographic images of quantitative parameters describing various features of brain hemodynamics, including CBF, CBV, oxygen extraction fraction (OEF) and cerebral metabolic rate of oxygen ($CMRO_2$). [84,95] The most frequently used PET tracer is ^{18}F fluorodeoxyglucose (FDG) for the detection of regional glucose consumption. PET studies generally show cerebral dysfunction beyond the structural abnormalities demonstrated by CT and MRI. [94,104-106] About one-third of these anatomical lesions are associated with more widespread metabolic abnormalities and as much as 42% of PET abnormalities were not associated with any anatomical lesions. [107] Epidural and acute subdural hematomas cause extensive reduction in metabolism in both the involved adjacent cortex and the corresponding contralateral cortex. DAI causes widespread hypometabolism, predominantly in the parieto-occipital cortex. [104,107] The period of metabolic reduction typically persists for several weeks regardless of injury severity. [108]

In the acute phase of mild TBI a normal FDG PET but an abnormal frontoparietal cortical brain perfusion was found using SPECT. This suggests that oedema and vasospasm secondary to mild TBI causes decreased perfusion detected by SPECT but that is not severe enough to impair glucose uptake. [109] In patients with mild to moderate TBI, a good correlation between severity of injury as measured by the GCS and the extent of whole brain metabolism was demonstrated, especially in patients with a GCS of 13 or lower. [94,110]

In the chronic phase after mild TBI, there are inconsistencies in PET findings varying from regional hypometabolism to global hypo- and hypermetabolism. [105,111] Chen and colleagues found no difference in cerebral FDG uptake between patients with mild TBI and controls in the resting state. [112] In patients with mild to moderate TBI with postconcussive symtpoms there is a correlation between complaints and the number of PET metabolic abnormalities, although both hypometabolism and hypermetabolism were seen in the same regions across different patients with mild TBI. [111] In patients with mild TBI and postconcussive symptoms, a high incidence of temporal lobe injury is visible on FDG-PET, [113] with a good association between PET abnormalities and neuropsychological assessment. [94,105,114] Global and regional metabolic rates improve as patients clinically recover from head trauma. [104,106,107]

Besides glucose metabolism, information from PET imaging on CBF in patients with TBI is also obtained with $H_2{}^{15}O$, $C^{15}O$ and $^{15}O_2$ tracers. Information on patients with mild or moderate TBI is scarce. Coles and colleagues showed that the extent of ischemic brain volume correlated with a poor outcome as measured with the Glasgow Outcome Scale (GOS) six months after injury. [115] In addition, a PET study of patients with moderate to severe TBI revealed the use of altered functional neuroanatomical networks when performing memory tasks,[116] whereas patients with mild TBI had a small increase in CBF in the right prefrontal cortex, compared with that in healthy people, during a memory task. [112] Although quantitative data can be obtained with PET and it offers a better resolution than SPECT, the application of this technique is limited by radiation exposure and scarce availability due to high costs. It is mainly used as a research tool in a non-emergency setting. [94]

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) offers a unique approach for assessing the metabolic status of the brain in vivo. In particular, this technique provides a non-invasive means for quantifying numerous metabolites such as N-acetylaspartate (NAA), creatine (Cr), choline (Ch) and lactate. [117] Of particular importance is NAA, because it is considered a marker of neuronal injury or loss. NAA is found to be decreased in cerebral contusions [118] and in the corpus callosum. [119] NAA concentrations in grey matter were predictive of overall neuropsychological performance in patients with moderate to severe TBI. [120] Moreover, a decreased NAA/Ch ratio is related to injury severity and outcome even when white matter appears normal on MRI (Figure 6). [121,122] Son and colleagues showed that in patients with mild TBI the NAA/Cr ratio was

low in areas of pericontusional oedema. Moreover, the lactate/creatine ratios were high in these areas, suggestive of ischemic damage. [123] Patients with good recovery, as measured by the Glasgow Outcome Scale (GOS), have high NAA/Cr ratios. [124] Despite these positive results, other researchers have found no associations between metabolic ratios and outcome at six months in individuals with mild TBI. [125] Choline, a marker for cell membrane disruption and inflammation, was high in the normal-appearing frontal white matter, [121,122] grey matter, [120,126] and parieto-occipital white matter. [126] Friedman and colleagues showed that increased choline concentrations in grey matter were not related to neuropsychological outcome at six months post injury, [120] contrary to another MRS study which revealed that elevated choline in both white and grey matter at three months post injury was significantly related to poorer outcome. [127] Although MRS provides a rapid way to assess in vivo brain composition, the interpretation of results is hindered by reliance upon ratios in various brain regions. Furthermore, the technique has a poor resolution, only partial brain coverage and its use is limited in the acute phase of TBI.

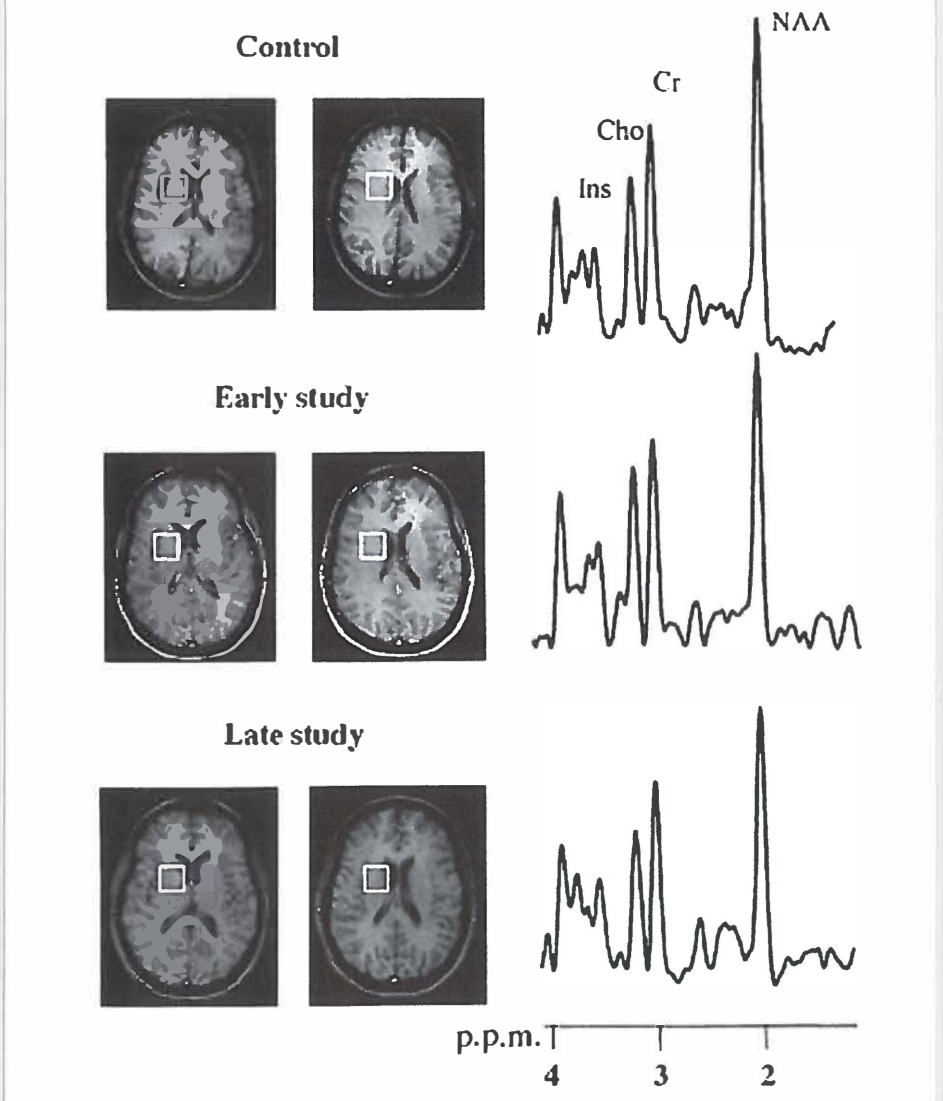

Figure 6. Magnetic resonance spectroscopy.
A 19-year-old female who was involved in a motor vehicle accident. Her initial Glasgow Coma Score (GCS) was 11. Early MRI (i.e. 18 days after injury) showed no abnormalities, while magnetic resonance spectroscopy (MRS) revealed a low NAA/Cr ratio with a high Cho/Cr ratio, compared with a healthy person. At the late study (i.e. 8.1 months after injury) conventional MRI remained unremarkable while there was a further decrease in the NAA/Cr ratio, compared to the early study.
(Published with permission of Oxford Journals and Dr. P. Style, originally published in Brain 2000;123:2046-2054).

Functional MRI

Functional MRI (fMRI) is a non-invasive technique in which blood oxygen changes serve as an endogenous contrast agent. Most current fMRI studies are based on the blood-oxygen-level-dependent (BOLD) method, in which the MRI signal derives from local changes in the ratio of deoxygenated to oxygenated hemoglobin that accompany neuronal events. Deoxyhemoglobin and oxyhemoglobin differ in their magnetic properties, so the changes in their relative proportions results in a temporary change in the MR signal of the target region relative to surrounding tissue. [128] Functional MRI is a promising technique because it combines the anatomical precision of MRI with functional information. Activation of brain regions involved in a particular language or cognitive task can be mapped, thereby increasing our knowledge of neuropsychological dysfunction. To date, standardised imaging protocols for fMRI have been developed mainly for the assessment and visualisation of brain regions involved in cognition and behaviour. In severe TBI, fMRI displays a more regionally dispersed pattern of cerebral activation, lateralised to the right hemisphere. [129,130] In a study on head injuries of various severity, altered brain activation was seen, suggesting that altered neural networks mediate cognitive control after TBI, possibly as a result of DAI.[131] In patients with pure DAI, compensatory activation of the prefrontal region was seen in comparison to healthy control subjects. [132] McAllister and colleagues used fMRI in patients with mild to moderate TBI to probe working memory function (i.e. the ability to retain information and to manipulate it in reaction to newly incoming material) within about one month after injury [133] and in some cases one year later. [134] Patients with TBI differed from control subjects in the activation pattern of working memory circuitry, with significantly higher activation on fMRI during moderate working memory load conditions, especially in the parietal and prefrontal regions. Task performance did not differ between patients and controls, suggesting that injury-related changes to modulating working memory might underlie some of the memory complaints after mild TBI. [128,133,134] In a study of concussed athletes with mild TBI, patients had low activation in the right prefrontal cortex compared with healthy controles on a memory task. [135] However, in football players, increases in amplitude and extent of activation patterns were demonstrated, predominantly in parietal, lateral frontal and cerebellar regions after a motor sequencing task in the absence of a decline in neurobehavioral performance. [136]

Functional MRI is a promising diagnostic imaging modality for the assessment of cognitive, task-related dysfunction in the chronic phase after TBI. Functional MRI has the advantage over imaging techniques such as PET and SPECT because multiple sessions can be done on a single subject in a short period of time. These features promote prospective studies with baseline measures of neurological function. Furthermore, fMRI holds great potential for widespread research and clinical use because it does not require exposure to ionising radiation. Application of this technique is best in the chronic phase when the patient is cooperative and able to comprehend test instructions.

NEW TECHNIQUES

Magnetoencephalograhpy (MEG) is a new technology that is based on the detection of magnetic field potentials, which permits real-time direct assessment of brain electrophysiology. MEG is superior to standard electroencephalography (EEG) as it provides more precise temporal and spatial patterns that are free from artefacts. The source of the EEG abnormality can be localised by MEG and registered on a standard MRI. As such, this technique is not a common imaging technique but provides a combination of a measure of electrophysiological dysfunction with anatomical information. [137]

MEG technology is used as a clinical diagnostic procedure for epilepsy and experimental research on sensimotor and language function. [138-140] It also provides useful information for the assessment of cognitive complaints. [141] In a study of TBI patients with postconcussive symptoms, the combined use of MEG and MRI resulted in the detection of abnormal activity in 65% of patients compared to 10% in asymptomatic patients. [142] The level of functional damage in patients with TBI far exceeds the area of focal damage depicted with structural imaging. To date, clinical studies with MEG are limited and it is too early to draw any conclusions relating to its potential use in TBI. Additional limitations for its use in a routine setting include costs and specialised requirements for housing these systems as a result of the need to shield the magnetic noise.

In summary, functional imaging techniques depict more and larger areas of abnormalities compared to structural imaging techniques in patients with TBI. Although functional imaging in patients with severe TBI patients has proven to be of prognostic value, there are few data concerning patients with mild to moderate TBI.

CONCLUSIONS

We have assessed various structural and functional imaging techniques in a clinical setting to guide management and to provide prognostic information on mild to moderate TBI (Tables 1 and 2). General problems that apply to imaging in patients with mild to moderate TBI are the heterogeneity of the population in terms of the extent, type and location of injury. Distinction has to be made between management in the acute phase after injury when the varying cooperation in agitated or confused patients interferes with rapid assessment and the investigation of symptoms and abnormalities in the chronic phase.

Tabel 1. Imaging techniques in mild to moderate traumatic brain injury: properties and feasibility.

Imaging techniques	Emergency setting	Brain coverage	Spatial resolution	Quantification	Contrast/ radiopharmaceutical	Radiation exposure	Costs	Clinical value
Structural								
CT	yes	whole	high	not applicable	no	yes	low	established
MRI conventional	restricted	whole	high	not applicable	no	no	intermediate	established
MRI DWI / ADC	restricted	whole	medium	yes	no	no	intermediate	under investigation
MRI DTI	restricted	whole	medium	yes	no	no	intermediate	under investigation
Functional								
SPECT	limited availability	whole	low	restricted	yes	yes	intermediate	not routinely used
Perfusion-MRI	restricted	whole	medium	restricted	yes	no	intermediate	under investigation
Perfusion CT	yes	partial	medium	yes	yes	yes	low	under investigation
PET	no	whole	low	yes	yes	yes	high	not routinely used
MRS	restricted	partial	low	yes	no	no	intermediate	under investigation
Functional MRI	restricted	whole	high	no	no	no	intermediate	under investigation

Abbreviations: MRS = magnetic resonance spectroscopy, DWI = diffusion weighted imaging, ADC = apparent diffusion coefficient DTI = diffusion tensor imaging, SPECT = single emission computed tomography, PET = positron emission tomography.

In the management of TBI, conventional CT is the imaging modality of first choice in the acute phase. CT is the most relevant imaging procedure for the detection of lesions eligible for surgical intervention and it is rapidly and easily performed. However, a normal CT on admission does not preclude brain injury and is of limited prognostic value. Although MRI is superior to CT in detecting DAI and non-hemorrhagic contusions, this technique is not easily applicable in the acute phase of TBI due to the limitations in monitoring patients during MRI and the susceptibility to motion artefacts related to the relatively long exposure time. Furthermore, there is no evidence that additional MRI affects neurosurgical management in patients with TBI. In general, within one to three months after injury, MRI assessment is preferable to other approaches if the appropriate sequences are used for the detection of posttraumatic abnormalities. Recently developed MRI techniques such as DWI and DTI are promising as they provide more insight into

the pathophysiological mechanisms of TBI. However, their prognostic value is unknown. Functional imaging modalities can provide useful information for determining the extent of ischemic and metabolic injury in patients with TBI. The main imaging techniques dedicated to brain hemodynamic and metabolism in TBI are MRS, fMRI, SPECT and PET. In general, SPECT and PET seem to be more sensitive in lesion detection compared to structural imaging techniques such as CT and MRI. Both imaging techniques have limited availability and are mainly used in a research setting. MRS and fMRI combine the accuracy of MR imaging with information on brain function and the metabolic state of the brain and are preferably used in the chronic phase after injury. The use of perfusion MRI and perfusion CT is not extensively investigated in TBI. Perfusion MRI provides better brain coverage than does perfusion CT, although this latter technique has some promising qualities, despite its radiation exposure, as it has a low exposure time and is readily available in most emergency departments. If it becomes more ready available, MEG may be a promising neuroimaging technique in the future. This new technique provides information on neuropsychological and neurobehavioral outcome in combination with anatomical studies.

Tabel 2. Imaging modalities and outcome studies comprising mild to moderate traumatic brain injury.

Author	Imaging Modality	Source Population	Phase Imaging	Outcome Measure	Time Outcome Assessment	Prognostic Value
Wardlaw, 2002[40]	CT	GCS 3-15, n = 425	Admission	GOS	1 year	Subarachnoid blood and overall CT appearance.
Kido, 1992[43]		GCS3-15, n = 72	Admission	GOS	6 months	Lesion size
Naalt van der, 1999[39]	MRI	GCS 9-14, n = 63	Early: 1-3 months Late: 6-12 months	GOSE	1 year	Lesions on early MRI, frontotemporal atrophy on late MRI
Yanagawa, 2000[56]		GCS 5-15, n = 34	< 3 weeks	GOS	3 months	Total number of lesions on T2*-GRE
Scheid, 2003[57]		GCS3-15, n = 66	3-292 months	GOSE	> 6 months	No
Hughes, 2004[58]		GCS 13-15, n = 80	1-3 days	Symptoms and RTW	6 months	No
Schaefer, 2004[70]	DWI	GCS 3-15, n = 26	< 2 days	Modified Rankin Score	Discharge	Volume of lesions
Huisman, 2004[72]	DTI	GCS3-15, n = 20	≤ 7 days	Modified Rankin Score	Discharge	Fractional anisotropy internal capsule and splenium
Hofman, 2001[60]	SPECT	GCS 14 -15, n = 21	2-5 days	Neurocognitive examination	2 and 6 months	No
Gowda, 2006[90]		GCS13-15, n = 92	< 3 days	Postconcussion syndrome	≤ 1 weeks	Perfusion abnormalities
Garnett, 2001	Perfusion MRI	GCS 3-15, n = 18	2-19days	GOS	6 months	Reduced CBV
Bergsneider, 2001[108]	FDG-PET	GCS 3-15, n = 13	Early: < 39 days Late: 6-15 months	DRS	Discharge, 6 and 12 months	No
Garnett, 2000[121]	MRS	GCS 3-15, n = 26	Early: 3-35 days Late: 3-11 months	GOS and DRS	3-11 months	Lowered NAA/Cr ratio obtained at early MRS

Abbreviations: MRS = magnetic resonance spectroscopy, DWI = diffusion weighted imaging, DTI = diffusion tensor imaging, SPECT = single emission computed tomography, FDG-PET = 18F fluorodeoxyglucose positron emission tomography, GCS = Glasgow Coma Score, GOS(E) = Glasgow Outcome Scale (extended), DRS = disability rating scale, RTW = return to work, GRE = gradient recalled echo, NAA=N-acetyl aspartase, Cr = creatinine.

New technologies adding a functional dimension to structural imaging are likely to improve the relationship between neuroimaging and outcome as they provide an index of hemodynamic and metabolic function in addition to anatomy. Additional studies are needed to assess the extent and duration of abnormalities found in symptomatic and asymptomatic patients. The potential ability of new MRI techniques to visualise axonal injury as the major pathological substrate of TBI is promising. The ability of functional neuroimaging to depict brain activity during cognitive tasks will enable the possibility to determine the efficacy of various rehabilitation programs. Further studies of mild to moderate TBI are necessary to prove the feasibility of neuroimaging for this patient group, as management is increasingly directed by the demand for imaging techniques which provide information that can guide clinical management and help to determine prognosis.

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Chapter

3

Perfusion computed tomography in the acute phase of mild traumatic brain injury: regional dysfunction and prognostic value

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ABSTRACT

Traumatic brain injury (TBI) is a major cause of disability and death. Most patients sustain a mild TBI with a subgroup that experiences disabling symptoms interfering with return to work. Brain imaging in the acute phase is not predictive of outcome, as 20% of non-contrast computed tomography (CT) scans on admission are normal in patients with a suboptimal outcome.

The aim of this study was to perform perfusion CT imaging in the acute phase of mild TBI patients without intracranial abnormalities on the non-contrast CT, to assess whether these patients had cerebral perfusion abnormalities. Furthermore, the relation between perfusion CT parameters and severity of TBI and outcome is evaluated.

In patients with mild TBI and a normal non-contrast CT, perfusion CT was performed directly after admission. The perfusion data were compared with data of twenty-five healthy control subjects. Outcome was determined six months after injury with the extended Glasgow Outcome Scale (GOSE) and return to work (RTW).

Seventy-six patients were included. In patients with a decreased Glasgow Coma Score, a significant decrease of cerebral blood flow (CBF) and cerebral blood volume (CBV) was detected in the frontal and occipital grey matter. In logistic regression analyses, decreased CBF and CBV in the frontal lobes predicted worse outcome according to the GOSE. CT perfusion parameters did not predict RTW.

In the acute phase of mild TBI, disturbed cerebral perfusion is seen in patients with a normal non-contrast CT correlating with severity of injury and outcome.

INTRODUCTION

Traumatic brain injury (TBI) is an important cause of disability and death in young adults, although the majority (80-90%) is classified as mild TBI. [1-5] Most of these patients recover within weeks to months without specific therapy. However, a subgroup continues to experience disabling symptoms that interfere with their return to work or resumption of social activities. [6-10] These symptoms not only cause a personal but also a social economical burden, since it often affects young patients in their twenties and thirties with full occupational status. It is of paramount importance to identify those patients who are prone to develop cognitive disability in order to institute early rehabilitation. [5,11,12] One of the first and most commonly used imaging techniques in the acute phase of TBI is non-contrast computed tomography (CT). It is used for the detection of hemorrhage, parenchymal injury and skull fractures. It is the most relevant imaging procedure for the detection of lesions eligible for surgical intervention as it is widely accessible, rapidly and easily performed, even in agitated patients. [13-15] The overall sensitivity of CT for the detection of abnormalities in acute TBI is estimated at 63-75%. [16,17] However, approximately 20% of the patients who sustain mild to moderate TBI without abnormalities on the admission non-contrast CT, experience problems with resuming work. [17] Advances in neuroimaging techniques may improve insights in the pathophysiology of TBI, increase the sensitivity for detecting abnormalities and hence allowing the development of better prognostic indicators. Perfusion CT is a functional imaging technique that makes use of the dynamics of iv-injected contrast material distribution. It has recently shown an increasing applicability in several patient categories, including stroke, [18-22] subarachnoid hemorrhage [23,24] and TBI. [25-27] In an increasing number of hospitals perfusion CT is applicable in the emergency setting and it can easily be combined with the non-contrast CT. The purpose of this study was twofold: first, to compare the cerebral perfusion of mild TBI patients with healthy control subjects, in relation to severity of TBI as estimated by the Glasgow Coma Score (GCS); and second, to determine the predictive value of cerebral perfusion in relation to outcome.

METHODS

Patients

Between May 2005 and June 2007, consecutive patients admitted with acute TBI were prospectively identified for enrolment in this study. Inclusion criteria were (1) age 18 to 65 years, (2) mild TBI defined as an initial GCS from 13 to 15 and (3) posttraumatic amnesia (PTA). After arrival at the emergency department, the GCS and duration of PTA were determined by the attending neurologist. None of the patients received sedation before admission to the emergency department. Patients with a history of neurological or psychiatric disease, mental retardation, addiction to alcohol or drugs or inability for long-term follow-up were excluded. Pregnancy, a history of diabetes, nephropathy and contrast allergy was additional exclusion criteria. A written informed consent was obtained from patients, family or next of kin if patients were unable or inadequate to provide consent. The control group consisted of twenty-five healthy volunteers (10 males and 15 females), with a mean age of 37 years (SD 12.2). All healthy control subjects fulfilled the same exclusion criteria as the patient group and gave their written informed consent. Both studies in patients and healthy control subjects were separately approved by the Medical Ethical Committee (METC) of the University Medical Center Groningen.

Imaging

The CT scans were made on a Siemens Somatom Sensation 64-row CT scanner (Siemens Medical Systems, Erlangen, Germany). The same scanning protocol was applied to all trauma patients and healthy control subjects. First, a standard non-contrast CT of the brain was performed, followed by a perfusion CT. In our patient group, the non-contrast CT scans were all evaluated by a radiologist on call. A central re-review was performed within a few days after trauma by an experienced neuroradiologist (L.R.). In this part of the study, we only analysed patients without intracranial abnormalities on the non-contrast CT. Two adjacent 14.4 mm thick slabs, perpendicular to the hard palate, were positioned at the level of the thalami, basal ganglia and third ventricle and at the level of the centrum semiovale and the lateral ventricles. A 40-ml volume of a non-ionic iodinated contrast agent (Visipaque 270 mg/mL) was power-injected at a rate of 5 ml/s, followed by a 20-ml saline chase. After 5s delay, a dynamic scan was initiated with the following parameters: 80 kV, 100 mA, and 1 s per rotation for a duration of 46 s. The estimated radiation dose was acceptable to the standards of our Medical Ethical Committee. Post-processing was also performed by experienced neuroradiologist (L.R.) using TeraRecon perfusion software (TeraRecon Inc., San Mateo, CA). A Gamma variate fitting curve was applied. The deconvolution algorithm produced two sets of colored parameter maps for cerebral blood flow (CBF), mean transit time (MTT) and cerebral blood volume (CBV). By using a digitally saved preset of regions of interest (ROIs) quantitative values for CBF, MTT and CBV were generated in the frontal, temporal and occipital white and grey matter (Figure 1).

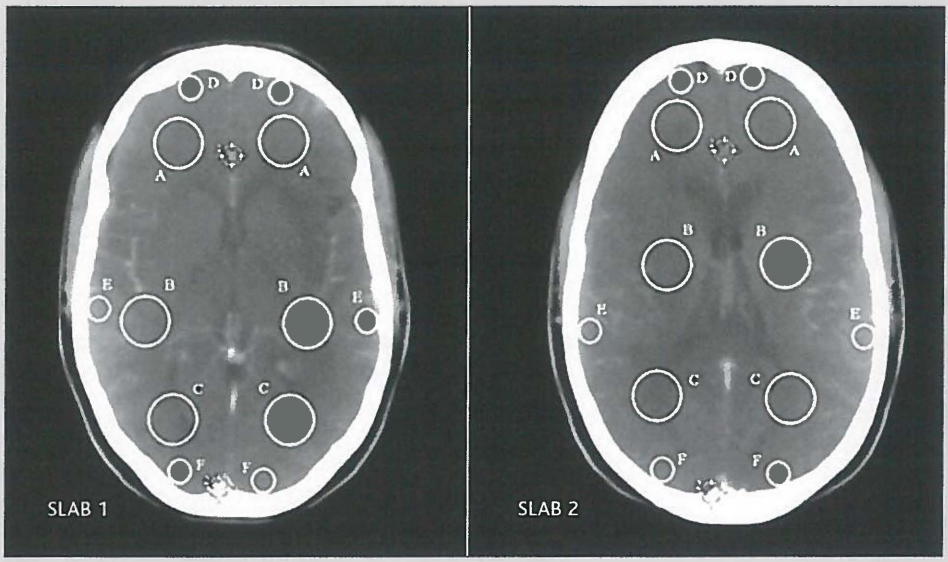

Figure 1. Two slabs with regions of interest (ROIs).
In each slab six ROIs were placed in the white matter (WM) and six ROIs were placed in the cortical grey matter (GM). A = frontal white matter, B = temporo-parietal frontal white matter, C = occipital white matter, D = frontal grey matter, E = temporo-parietal grey matter, F = occipital grey matter. Slab 1 is the lower slab; slab 2 is the upper slab.

Outcome

At 6 months after injury the outcome was determined with two outcome measures: the extended Glasgow Outcome Scale (GOSE) and return to work (RTW). First, the GOSE was used, [28] which comprises eight outcome categories: 8 = good recovery; 7 = good recovery with minor physical or mental deficits; 6 = moderate disability, return to previous work with some adjustments; 5 = work at a lower level of performance; 4 = severe disability, for some activities dependent on others; 3 = severe disability, completely dependent; 2 = vegetative state; and 1 = death. We dichotomised outcome as optimal (GOSE = 8) and suboptimal (GOSE < 8). RTW comprises four categories: 0 = previous work or study resumed; 1 = previous work or study resumed, but with lower demands or part-time; 2 = previous work or study not resumed, different work on a lower level; 3 = not working. We also dichotomised RTW as optimal if patients completely resumed their previous work or activities, and suboptimal if patients resumed their previous work on a part-time basis or lower level, or if they could not resume their previous work. The outcome was measured by a neurologist (J.v.d.N.), who was unaware of perfusion CT results at 6 months after injury in our outpatient clinic. The GOSE was evaluated by a structured interview according to suggested guidelines. [29]

Statistical analysis

All statistical analyses were done using SPSS (Statistical Package for the Social Sciences) version 16.0 (SPSS, Chicago, IL). Perfusion data from the left and right hemispheres and both slabs were averaged. To compare cerebral perfusion between patients and healthy control subjects, between patients with a GCS of 15 and less than 15 and between those with an optimal and a suboptimal outcome, we calculated comparances with analysis of variance (ANOVA). These analyses were stratified by the three perfusion parameters (CBF, MTT and CBV) and the six anatomical regions in the frontal, temporal and occipital white and grey matter. The presented P-values were adjusted for age and gender. For calculating the predictive value of cerebral perfusion values, logistic regression analysis was applied, as dichotomised outcome measures were evaluated. The suboptimal outcome for GOSE and RTW were used as the reference categories. Statistical significance was defined as P-value < 0.05.

RESULTS

Patient characteristics

A total of 95 patients fulfilled the inclusion criteria of which no intracranial abnormalities on the non-contrast CT were seen in 76 patients. In this part of the study only patients without intracranial abnormalities on the non-contrast CT were analysed. Patient characteristics are displayed in Table 1. Data concerning outcome are missing in 1 patient. The mean time between injury and perfusion CT scanning was 3.9 hours (SD 2.2). Perfusion CT scanning was always completed without complications, and no adverse reactions to the contrast material occurred. The mean systolic and diastolic blood pressure at admission (N = 58) was 136.6 and 77.9 mmHg, respectively. Pulmonary injury was present in three patients, and one patient had an abdominal injury. None of the patients were circulatory instable or were mechanically ventilated. In total, 12 patients had fractures of the extremities (4), ribs (4) and spinal column (4). In addition, 1 patient had a skull and skull base fracture, 2 patients had a skull base fracture and 10 patients had fractures of the facial bones.

Table 1. Patient characteristics.

Patient characteristics (N = 76)		
Mean age in years, mean (SD)		35.0 (14.0)
Male		57 (75.0)
Traffic accidents		49 (64.5)
GCS, mean (SD)		14.2 (0.5)
	15	22 (29)
	14	50 (65)
	13	4 (5)
Duration PTA in hours, mean (SD)		9.0 (22.2)
GOSE, mean (SD)#		7.3 (0.79)
	8	36 (48)
	7	26 (35)
	6	12 (16)
	5	1 (1)
Return to work #	Complete	59 (78.7)
	Parttime	13 (17.3)
	Lowerlevel	1 (1.3)
	No	2 (2.7)

Abbreviations: GCS = Glasgow Coma Score, PTA = posttraumatic amnaesia, GOSE = extended Glasgow Outcome Scale. SD = standard deviation. Values are number (%) unless noted otherwise.

N = 75

Patients versus healthy control subjects

When comparing global perfusion CT parameters, no significant differences were present. When comparing perfusion CT parameters between patients and healthy control subjects in different cerebral regions, a decreased MTT was present in the frontal white matter (4.42 vs 4.00 sec; P = 0.029) and grey (4.07 vs 3.80 sec; P = 0.038). The CBV was decreased in the occipital grey matter (3.07 vs 2.90 ml • 100 g^{-1}; P = 0.019) in our patient group. No significant differences in perfusion CT parameters were detected in the temporal-parietal areas.

Cerebral perfusion and severity of injury

For evaluation of perfusion data in relation to severity of TBI, the patient group was dichotomised into those with a GCS of 15 and those with a GCS less than 15, and also compared with healthy control subjects (Figure 2). The histograms represent the unadjusted values; the P- values are adjusted for age and gender. Patients with a GCS less than 15 had a significant lower CBF in the frontal and occipital grey matter, compared with healthy control subjects. Also, the CBV in the occipital grey matter was significantly lowered in this patient group. In patients with a GCS of 15 a significant higher CBF in the frontal and occipital white matter was seen, when compared to healthy control subjects.

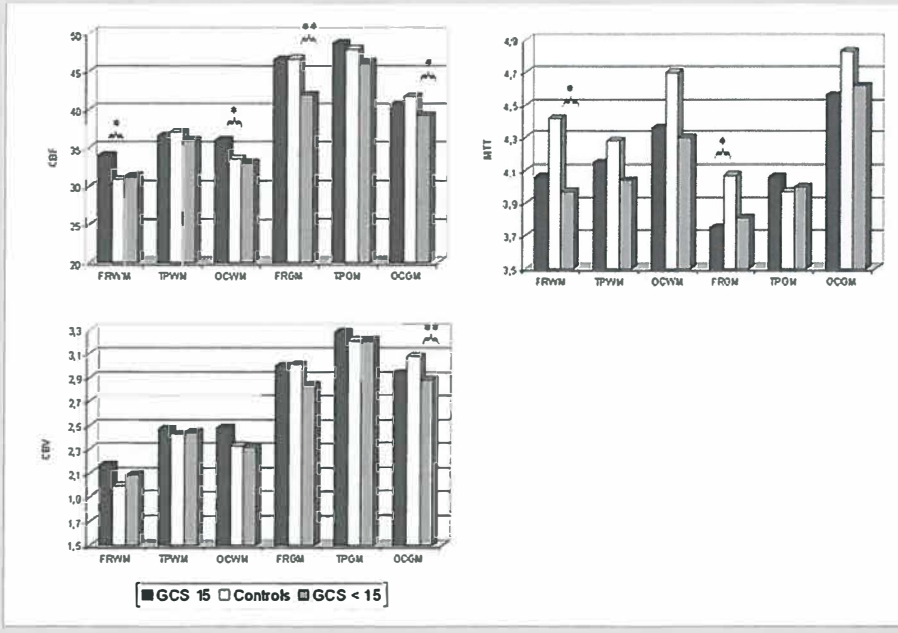

Figure 2. Cerebral perfusion parameters in patients with different injury severities compared to healthy control subjects.

CBF (cerebral blood flow), MTT (mean transit time) and CBV (cerebral blood volume) measured in healthy control subjects (white bars) and patients with a GCS (Glasgow Coma Score) of 15 (dark bars) and patients with a GCS less than 15 (grey bars) measured in different cerebral areas (FRWM = frontal white matter, TPWM = temporo-parietal white matter, OCWM = occipital white matter, FRGM = frontal grey matter, TPGM = temporo-parietal grey matter, OCGM = occipital grey matter). Data displays mean values.
* $P < 0.05$, ** $P < 0.01$, P-values are adjusted for age and gender effects.

Cerebral perfusion and outcome

Extended Glasgow Outcome Scale

The outcome was determined at 6 months after injury (mean 6.87 months, SD 1.61). Thirty-six (48%) patients had an optimal outcome according to the GOSE. Of the patients with a suboptimal outcome, 26 (34.7%) had a GOSE sumscore of 7, 12 (16%) patients scored 6 and 1 patient (1.3%) had a score of 5.

Figure 3 displays the differences in cerebral perfusion between patients with a GOSE of 8 and those with a GOSE less than 8. In patients with a suboptimal outcome according to the GOSE, the CBF and CBV were most significantly decreased in the frontal white and grey matter, compared to those with an optimal outcome. Logistic regression analyses showed that cerebral perfusion parameters predicted GOSE significantly in the frontal white and grey matter and the occipital grey matter (Table 2). MTT was not a significant predictor for outcome.

PTA, GCS and age predicted 17.0%, 13.7% and 1.6% of the variance, respectively. When dividing the patient group in those with a GCS of 15 and those with a GCS less than 15, the perfusion CT data were not predictive for the GOSE in the former group.

Return to work

Of the 75 patients, 59 (78.7%) resumed their previous work or activities completely. Consequently, approximately one in five patients resumed previous activities only partially, either on a lower level or not at all. When comparing patients who resumed their work completely with those resuming their occupation on a lower level, the latter group had a significant ($P = 0.040$) lower CBF in the frontal grey matter. Logistic regression analyses revealed that perfusion CT parameters are not independent predictors of RTW.

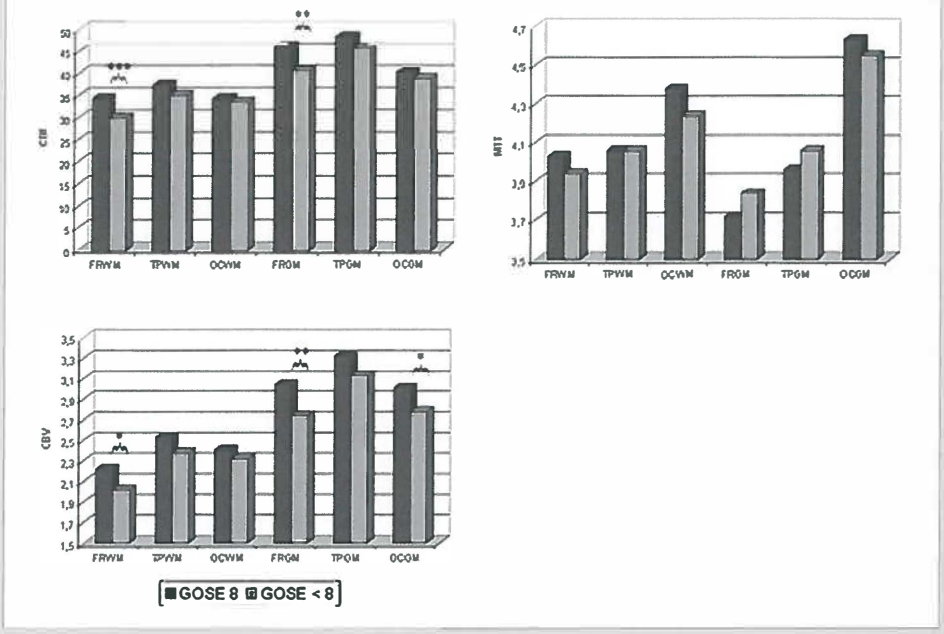

Figure 3. Cerebral perfusion related to outcome according to the extended Glasgow Outcome Scale (GOSE).

CBF (cerebral blood flow), MTT (mean transit time) and CBV (cerebral blood volume) measured in different cerebral areas (FRWM = frontal white matter, TPWM = temporo-parietal white matter, OWM = occipital white matter, FRGM = frontal grey matter, TPGM = temporo-parietal grey matter, OCGM = occipital grey matter) in patients with a GOSE of 8 (optimal; dark bars) compared with patients with a GOSE less than 8 (suboptimal; light bars). Data display mean values.

* P < 0.05, ** P < 0.01, *** P < 0.001, P-values are adjusted for age and gender effects.

Table 2. Logistic regression analysis: predictors of optimal extended Glasgow Outcome Scale.

		OR	95% CI	P	Nagelkerke Rsquare(%)
CBF	FRWM	1.230	1.09 - 1.38	0.001	26.1
	FRGM	1.160	1.06 - 1.27	0.002	22.0
CBV	FRWM	5.696	1.16 - 27.88	0.032	11.8
	FRGM	5.225	1.60 - 17.06	0.006	16.2
	OCGM	6.507	1.43 - 29.64	0.015	13.0

Abbreviations: CBF = cerebral blood flow, CBV = cerebral blood volume, FRWM = frontal white matter, FRGM = frontal grey matter, OCGM = occipital grey matter, OR = odds ratio, CI = confidence interval.

P-values are adjusted for age and gender effects.

DISCUSSION

In this study cerebral perfusion was measured in the acute phase of mild TBI patients without intracranial abnormalities on the non-contrast CT and compared with healthy control subjects. To our knowledge, this is the first study in which a perfusion CT was performed in the acute phase of patients with mild TBI. In this study, we observed no side effects related to iodinated contrast material administration like nephrotoxicity or allergic reactions.
The most relevant finding of this study was a significant difference of cerebral perfusion in patients with mild TBI compared with healthy control subjects, especially in relation with severity of injury. Furthermore, a relation with cerebral perfusion and outcome was found.

Cerebral perfusion parameters in patients compared with healthy control subjects
With the application of perfusion CT, a significant difference was present in cerebral perfusion between patients and healthy control subjects, related to severity of injury with differentiation between grey and white matter.
In the acute phase of mild TBI, a small number of hemodynamic imaging studies have been performed using radiotracer methods such as single photon emission computed tomography (SPECT) [30-33] or Xenon-CT. [34] These studies also demonstrated perfusion abnormalities, mostly hypoperfusion, predominantly in the frontal and temporal lobes, basal ganglia and thalami and to a lesser extend in the occipital lobes. [30-32] As opposed to our study, these aforementioned studies only measured global perfusion, and hence did not differentiate between white and grey matter areas. Furthermore, scanning procedures with radiotracers are much more elaborate and therefore not easy applicable in the emergency setting as opposed to perfusion CT.
This study genuinely shows that the cortical grey matter is involved in this category of TBI.

Cerebral perfusion parameters and severity of injury
To answer the question whether the perfusion CT should be performed in each patient category with TBI, results were evaluated the results in different categories of severity. A relation between cerebral perfusion and severity of injury as measured by the GCS was present. The most prominent difference between patients with a GCS of 15 compared with those with a GCS less than 15, was the significant decrease of CBF and CBV in the frontal and occipital grey matter in the latter group. In contrast, patients with a GCS of 15 showed even a significantly higher CBF in the frontal white matter.
It remains questionable whether the reductions in CBF in the patients with a GCS less than 15 can also represent truly ischemia, or solely be due to reduced functional activity. The magnitude of 5-6% reduction in de occipital lobes may support the latter finding. [35] A comparison of changes in perfusion with concurrent changes in cerebral metabolism might provide further answers to this matter.

The question arises whether these changes in CBF could be a reflection of a difference in the level of agitation or drowsiness in the two patient groups. However, this explanation would only account for the occipital lobes as it is known that in visual tasks an increase up to 10% of the perfusion in the occipital lobes is seen. [36] Another explanation for the increased CBF in patients with higher GCS could be a compensatory vasodilatation in the intraparenchymal vessels as a result of autoregulatory mechanisms. [37,38] Most studies examining the value of CBF and CBV are done in severe brain injured patients where high global CBF and CBV values are associated with intact autoregulation and favourable outcome. [25,39] Sakas and colleagues also demonstrated cerebral hyperemia in predominantly those with mild TBI, which was also associated with a favourable outcome. [40] Therefore, we hypothesise that, in our patient group, cerebral autoregulation resulted in hyperperfusion in the frontal white matter evoked by cortical traumatic impact.

Cerebral perfusion parameters and outcome

The value of perfusion CT in relation to outcome was determined by the GOSE and RTW. As outcome in this patient category mostly concerns the upper range of the GOSE, patients with optimal outcome were compared to those with suboptimal outcome, defined by a GOSE of 8 and less than 8, respectively. Significant decreases in CBF and CBV were found in patients with a suboptimal outcome according to the GOSE, predominantly in the frontal lobes. In a logistic regression analysis these parameters were predictive of outcome according to the GOSE in patients with a GCS less than 15, in addition to already known predictors of outcome such as age and duration of PTA. [7,41] Especially the reduced CBF in the frontal lobes and its relation with outcome is an interesting finding. Research in mild TBI currently is more focused on executive problems related to frontal lobe dysfunction. [42] An interesting future theme to explore could be the relation between frontal lobe dysfunction as measured with neuropsychological tests and CT perfusion parameters. Furthermore, because perfusion parameters were not predictive for outcome in those with a GCS of 15, the applicability of the perfusion CT seems most valuable in patients with a GCS of at least 14.

Few prognostic hemodynamic imaging studies comprising mild TBI patients have been performed. The negative predictive value of a normal initial SPECT has been established in these patients. [43-45] Garnett and colleagues also showed, with perfusion MRI, that patients with a reduced CBV in normal-appearing brain had a worse clinical outcome than patients without abnormalities, [46,47] which is in line with our results. Wintermark and colleagues performed the only prognostic perfusion CT study in TBI patients. They revealed that in severe TBI, a reduced CBF and CBV on admission was also predictive of outcome. [25]

In contrast to GOSE, perfusion CT findings did not predict RTW. In this study, almost 80% of the patients had a complete resumption of their previous work, although more than half of them experienced residual complaints and had a suboptimal outcome according to the GOSE. These

complaints and other patient-related factors, such as anxiety and depression, should be evaluated in more detail to elucidate their role in resumption of work.

Applicability and Limitations

Perfusion CT is easily applicable in the acute phase of TBI, because of its short examination time and 24 hour availability in a rising number of hospitals.

In this study, we observed no side effects related to iodinated contrast material administration such as nephrotoxicity or allergic reactions. In an early stage, information is provided facilitating development of more support for some patients otherwise prone to develop cognitive disabilities. With the introduction of a new technique, however, one has to be aware of potential disadvantages, for instance, the exposure to additional radiation. With the development of more advanced technical systems, the radiation exposure is within acceptable limits, comparable with a standard CT. Certainly, the use of perfusion CT should be limited to those patients who are expected to benefit from the introduction of this new imaging technique. Although more research is needed, so far the applicability seems to be limited to patients who have a normal CT scan on admission with at least a GCS of 14 or less. Given the fact that most mild TBI patients arrive at the hospital with a GCS of 15 these restrictions would prevent an enormous increase of perfusion CT imaging that could negatively interfere with daily routine of TBI patients.

The technical limitations that should be mentioned are the restricted area and positioning of the slabs. Although complete brain coverage is not possible with perfusion CT imaging, data are obtained from the regions frequently involved in this category of patients, namely, the frontotemporal region at the base of the skull. When positioning the slabs to low, one has to be aware of the partial volume effects from the skull. Furthermore, compared with the literature, our white matter values are relatively high, also in our healthy control subjects. This is most likely due to the fact that it is technically difficult to obtain pure white matter samples, especially at the temporal areas at the level of the third ventricle. Also, it could be stated that our grey matter values are relatively low. An explanation could be that the relatively small regions of interest in the cortical grey matter are more vulnerable to partial volume effects. Nevertheless, our observations are convincing as the same procedure was applied in both the patient group and the healthy control group, and therefore these values definitely can be compared with each other.

Conclusion

With the perfusion CT it is possible to detect abnormalities in patients with mild TBI with a normal non-contrast CT on admission. These abnormalities are predominantly present in the frontal and occipital lobes. The perfusion abnormalities are related to severity of injury as estimated by the GCS. In patients with a suboptimal outcome as measured with the GOSE, a significant decrease of CBF and CBV was present. The applicability and prognostic value of the

perfusion CT are more obvious in patients with a GCS less than 15. To establish the use of perfusion CT in daily routine, other studies are needed to confirm our results. Furthermore, the relation of perfusion CT parameters with complaints and neuropsychological data need to be more thoroughly investigated.

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Chapter

4

Acute cerebral perfusion CT abnormalities associated with posttraumatic amnesia in mild traumatic brain injury

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ABSTRACT

Posttraumatic amnesia (PTA) is a common symptom following traumatic brain injury (TBI). Although this transient memory deficit implies specific impairment of higher brain function, the actual pathophysiology of PTA is not well understood.

The aim of this study was to assess regional cerebral hemodynamics with perfusion computed tomography (CT) in patients during PTA following mild TBI compared to patients with resolved PTA.

A total of 74 patients with mild TBI without structural abnormalities on a non-contrast CT were included and compared to 25 healthy control subjects. Two patient groups were defined: (1) a PTA-group that was scanned during the episode of PTA (N = 34), and (2) a post-PTA-group scanned after resolution of PTA (N = 40). The PTA-group had a significantly reduced cerebral blood flow (CBF) in the frontal grey matter (41.78 (SD 7.4) versus 44.44 (SD 6.2) ml • 100 g^{-1} • min^{-1}, P = 0.023) and caudate nucleus (44.59 (SD 6.2) versus 47.85 (SD 7.7) ml • 100 g^{-1} • min^{-1}, P = 0.021), compared to the post-PTA group.

Thus in patients with mild TBI, PTA is associated with cerebral perfusion abnormalities in specific cortical and subcortical regions.

INTRODUCTION

Traumatic brain injury (TBI) is frequently followed by a transient state of anterograde amnesia accompanied by confusion and disorientation, referred to as posttraumatic amnesia (PTA).[1] The hallmark of this syndrome is reflected by an inability to store current events,[2] often in combination with restlessness and agitation after injury. It has been established that the duration of PTA in head injured patients is of prognostic significance,[3-5] particularly in mild to moderate TBI.[6] However, the pathophysiological basis of PTA is not well understood, and only a few studies have described patients during the amnestic state. Most functional imaging studies performed so far were not able to provide further insight in the neuronal mechanisms that underlie PTA, because most of the patients were examined after resolution of PTA, or information whether patients were examined during or after PTA was lacking. Furthermore, most hemodynamic imaging studies on PTA were performed with single-photon emission CT (SPECT), a semi-quantitative technique with low spatial resolution and restricted tracer availability.[7,8] With the increasing application of perfusion CT imaging in trauma patients,[9,10] it has become feasible to quantitatively assess cerebral perfusion parameters, particularly in the acute phase after injury. The objective of this study was to examine regional cerebral hemodynamics with perfusion CT imaging in patients with mild TBI, providing an index for local neuronal function, either during PTA or after the resolution of PTA. The results were compared with the cerebral hemodynamics of healthy control subjects.

METHODS

Patients

Patients with acute TBI were identified as candidates for enrolment in this prospective study during a 2-year period, between May 2005 and June 2007. Inclusion criteria were (1) age 18 to 65 years, (2) mild TBI defined as an initial Glasgow Coma Score (GCS) from 13 to 15, (3) the presence of posttraumatic amnesia (PTA) and (4) no intracranial abnormalities on the non-contrast CT. An earlier study published in 2009 comprised the same study population. [11] The duration of PTA was defined as the time between injury and return of orientation and continuous memory encoding. PTA was established prospectively by means of a questionnaire. [6] If the PTA had resolved before the patient arrived at our emergency department, its duration was estimated retrospectively. Two distinct groups were distinguished: (1) a PTA-group with patients who were scanned during their episode of PTA, and (2) a post-PTA-group with patients who were scanned after resolution of PTA. Patients with a history of neurological diseases, psychiatric disorders, mental retardation, addiction to alcohol or other drugs or ineligibility for long-term follow-up were excluded. Pregnancy, and a history of diabetes, nephropathy and iodine allergy were additional exclusion criteria. Written informed consent was obtained from patients or from either family or next of kin if the patients were unable to provide consent themselves. The control group consisted of twenty-five healthy volunteers (10 males and 15 females), with a mean age of 37 years (SD 12.2). Healthy control subjects fulfilled identical exclusion criteria as the patient group and also provided written informed consent. Both parts of the study, those addressing patients and healthy control subjects, were separately approved by the Medical Ethical Committee (METC) of the University Medical Center Groningen.

Imaging

Patients underwent imaging after admission at the emergency department immediately after consent was obtained. CT images were obtained by a Siemens Somatom Sensation 64-row CT scanner (Siemens Medical Systems, Erlangen, Germany). First a standard non-contrast CT was performed followed by a perfusion CT scan. Two adjacent 14.4 mm thick slabs were positioned at the level of the thalami, basal ganglia and third ventricle and at the level of the centrum semiovale and the lateral ventricles, and 40-ml of a non-ionic iodinated contrast agent (Visipaque 270 mg/ml) was power-injected at a rate of 5 ml/s, followed by a 20-ml saline infusion. After a 5-s prep delay, a continuous scan was initiated with the following parameters: 80 kV, 100 mAs, and 1 rotation per 1 s for a total duration of 46 s. Post-processing was performed by an experienced neuroradiologist (L.R.) using TeraRecon perfusion software (TeraRecon Inc., San Mateo, CA). A Gamma variate fitting curve was applied. The deconvolution algorithm produced two sets of colored parameter maps for cerebral blood flow (CBF), mean transit time (MTT) and cerebral blood volume (CBV). By using a saved preset of regions of interest (ROIs) quantitative

values for CBF were generated in the frontal, temporal and occipital white and grey matter, caudate nucleus and thalamus. The lower slab is displayed in Figure 1. The neuroradiologist (L.R.) who examined the perfusion CT images was not informed about the patient characteristics. No edatives were given during the procedure.

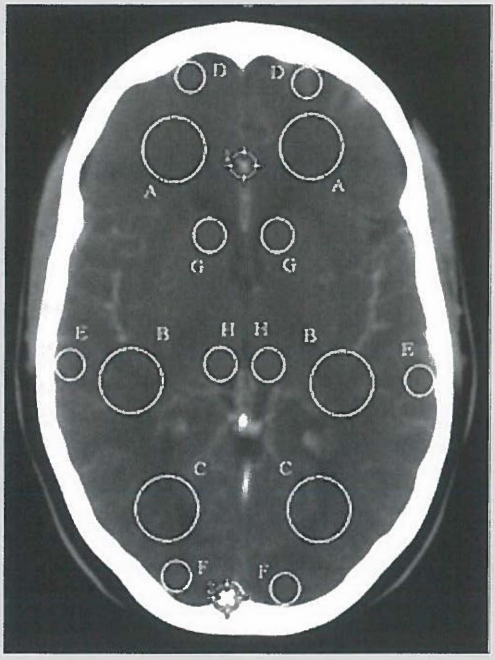

Figure 1. Regions of interest (ROIs).

Lower slab with ROIs. In this slab six ROIs were placed in the white matter (WM) and six ROIs were placed in the cortical grey matter (GM). Also two ROIs were placed in the caudate nuclei and two ROIs were placed in the thalami. A = frontal white matter, B = temporo-parietal white matter, C = occipital white matter, D = frontal grey matter, E = temporo-parietal grey matter, F = occipital grey matter, G = caudate nucleus, H = thalamus.

Statistical analysis

All statistical analyses were done using SPSS (Statistical Package for the Social Sciences Inc, Chicago, IL) version 16.0. Perfusion data from the two slabs were averaged. Analysis of variance (ANOVA) was used to compare CBF, MTT and CBV values of patients who were still in PTA during scanning (PTA-group) with those obtained from patients with resolved PTA (post-PTA-group). Patient data were also compared with a healthy control group. These analyses were stratified by the eight anatomical regions in the frontal, temporal and occipital white and grey matter, caudate nucleus and thalamus. The presented P-values were adjusted for age and gender by using them as covariates in the statistical analyses. Statistical significance was defined as P-value < 0.05.

RESULTS

Patient characteristics

Seventy-six patients fulfilled the initial inclusion criteria. A total of 74 patients were finally analysed, as in 2 patients it remained unsure if they were scanned during or after their period of PTA. Patient characteristics are displayed in Table 1. In the PTA-group 34 patients were included, and in the post-PTA-group there were 40 patients. In all patients, perfusion CT scanning was completed without complications, and no adverse reactions to the contrast material occurred. The mean time between injury and perfusion CT scanning was 3.9 hours (SD 2.2). Most injuries (63.5 %) were caused by traffic accidents, predominantly bicycle-related injuries (36.5 %). None of the patients suffered from circulatory instability or needed mechanical ventilation. Alcohol consumption prior to the accident was present in 28 patients, no intoxication was found. In 3 patients pulmonary injury was diagnosed, and one patient had an abdominal injury. In 10 patients fractures were present, distributed over the extremities (4), ribs (3) and spinal column (4) while 3 patients had a skull and/or skull base fracture, and 9 patients suffered from facial fractures.

Table 1. Patient characteristics.

Patient characteristics	PTA-group (N=34)	Post-PTA-group (N=40)
Time between injury-perfusion CT in hours (SD)	3.20 (1.3)	4.6 (2.6)
Mean age in years (SD)	30.8 (12.0)	38.9 (14.6)
Number of males (%)	28 (82.4)	27 (67.5)
Number of traffic accidents (%)	23 (67.6)	24 (60.0)
Mean GCS (SD)	13.9 (0.3)	14.5 (0.6)
Mean duration PTA in hours (SD)	15.8 (29.5)	1.9 (3.9)
Mean hematocrit in L/L (SD)	0.41 (0.05)	0.41 (0.04), N=39
Number of patients with alcohol consumption (%)	12 (35.3)	16 (40)

A division was made between those who obtained a perfusion CT during their period of posttraumatic amnesia (PTA-group) and those scanned after their period of PTA (post-PTA-group).
Abbreviations: GCS = Glasgow Coma Score, SD = standard deviation, CT = computed tomography.

PTA and regional perfusion abnormalities

Regional CBF, MTT and CBV values were obtained for both patient groups during or after the episode of PTA. The regional CBF values are displayed in Figure 2. Patients who were scanned during their period of PTA showed a significantly reduced CBF in both the frontal grey matter (41.78 (SD 7.4) vs. 44.44 (SD 6.2) ml • 100 g^{-1} • min^{-1}, P = 0.023) and the caudate nucleus (44.59 (SD 6.2) vs. 47.85 (SD 7.7) ml • 100 g^{-1} • min^{-1}, P = 0.021), compared to the post-PTA-

group. Furthermore, there was a significant correlation (R = 0.626, P < 0.001) between the CBF in the frontal grey matter and the caudate nucleus. The MTT in the thalamus was significantly increased in patients scanned during PTA (4.22 (SD 1.2) vs. 3.78 (SD 0.7) sec, P = 0.039). No significant relation between CBV and PTA was present.

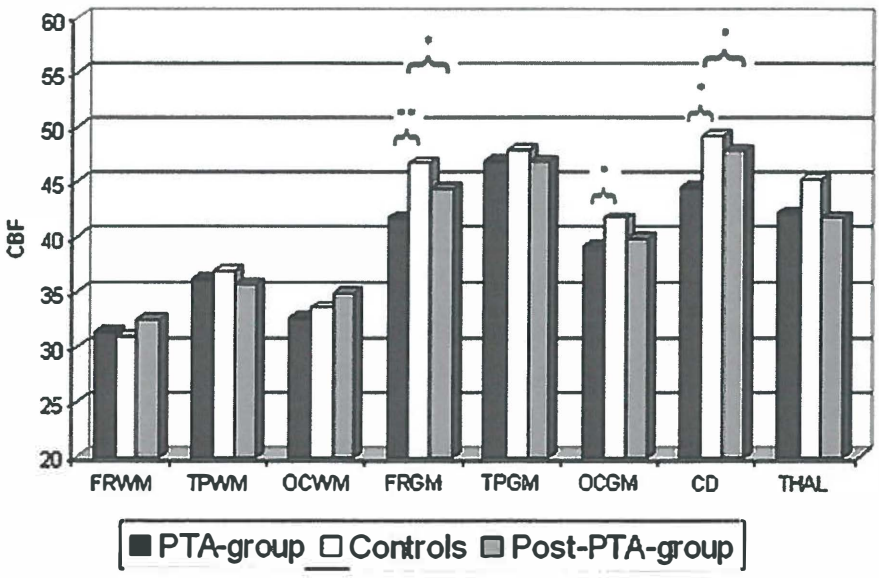

Figure 2. Cerebral perfusion and posttraumatic amnesia (PTA).
Differences are shown between patients who underwent a perfusion computed tomography (CT) during a period of posttraumatic amnesia (PTA-group; dark bars) and after their period of PTA (post-PTA-group; grey bars), compared with healthy control subjects (white bars) for cerebral blood flow (CBF) in different cerebral areas (FRWM = frontal white matter, TPWM = temporo-parietal white matter, OCWM = occipital white matter, FRGM = frontal grey matter, TPGM = temporo-parietal grey matter, OCGM = occipital grey matter, CD = caudate nucleus, THAL = thalamus). Data displays mean values.
* P < 0.05, ** P < 0.01. P-values are adjusted for age and gender effects.

When compared to healthy control subjects, a significant decrease in CBF in the frontal grey matter was observed in patients scanned during PTA (41.78 (SD 7.4) vs. 46.71 (SD 5.5) ml • 100 g^{-1} • min^{-1} respectively, P = 0.009). Significant, although less strong, decreases in CBF of the PTA-group compared to healthy control subjects were also found in the caudate nucleus and occipital grey matter. The MTT was significantly decreased in patients scanned during PTA compared to healthy control subjects (3.87 (SD 0.7) vs. 4.42 (SD 0.7) sec, P = 0.009), whereas

no significant differences in CBV could be discerned. In post-PTA patients, no significant differences in CBF in the various regions were found when compared with healthy control subjects.

A longer duration of PTA was associated with a significant decrease of CBF in the frontal grey matter (R = -0.330, P = 0.006), which was more pronounced in the right hemisphere. This relation is visualised in Figure 3. A cut-off point could not be discerned. No relation was present between the length of time between injury and scanning and CBF values. Alcohol consumption was neither related to changes in cerebral perfusion, nor did it influence the relation between cerebral perfusion and PTA.

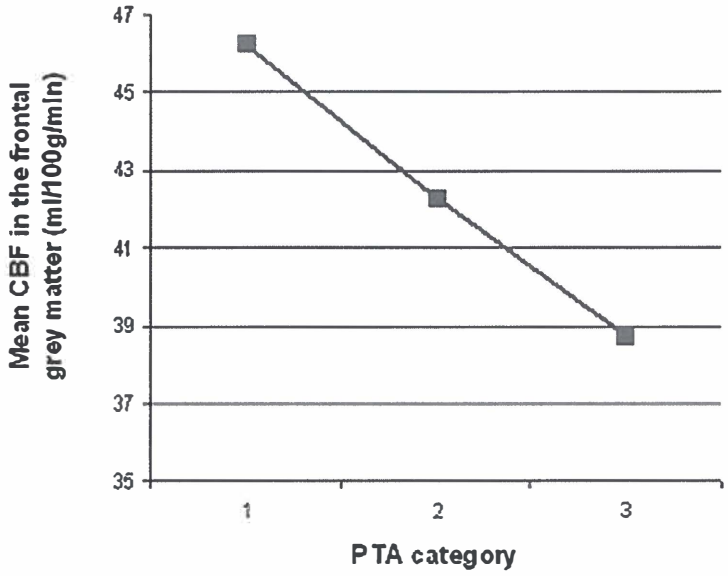

Figure 3. Cerebral blood flow (CBF) and duration of posttraumaic amnesia (PTA).
CBF in the frontal grey matter displayed on the Y-axis with duration of PTA divided in three categories on the X-axis (category 1: 0 -1 hour (N = 25); category 2: 1-12 hours (N = 41); category 3: > 12 hours (N = 8)).

DISCUSSION

In this study cerebral hemodynamics was studied with perfusion CT imaging in patients who were scanned either during or after PTA following mild TBI. During the amnestic state significant cerebral perfusion decreases were observed in the frontal grey matter and caudate nucleus, indicating locally impaired neuronal function in this patient category.

To our knowledge, no previous studies have addressed the hemodynamics in patients during and after their period of PTA, although with SPECT studies regional perfusion abnormalities have been observed in patients with a posttraumatic amnestic period and a normal non-contrast CT scan. The extent of these SPECT-abnormalities was found to be related to the duration of PTA, with hypoperfusion predominantly in the frontal and temporal lobes.[7,8] With Xenon-CT, abnormalities were also seen in the frontotemporal region in a small group of mild TBI patients with an amnestic period, compared to healthy control subjects.[12]

The pathophysiological mechanism of PTA is not well understood, and various mechanisms have been suggested, such as focal oedema, direct injury and ischemia, while even perfusion changes due to remote alteration of neuronal activity have been suggested.[1] The involvement of the temporal lobes, and the hippocampus in particular, in memory processes has been well described, as bilateral damage of these structures may cause severe anterograde amnesia.[13,14] However, it remains questionable whether the pathophysiological mechanism of PTA, which by definition is transient, may be extrapolated from conditions with permanent anterograde amnesia associated with structural abnormalities. The resolution of PTA suggests the presence of functional changes as opposed to structural changes. It is important to keep in mind that the patients examined in the current study were analysed either during or after an amnestic state but that in all our patients the PTA ultimately resolved.

A condition comparable to PTA is transient global amnesia (TGA), because of its temporarily stunned memory. TGA is characterised by transient anterograde amnesia. Involvement of various interconnected cerebral regions like the hippocampal formation, thalamus, cingulate gyrus, striatum, and cortices has been demonstrated.[15-18] CBF changes in various regions during TGA have a tendency to resolve spontaneously, whereas positron emission tomography (PET)-studies did not show signs of ischemia so far.[19] Schmidtke and colleagues demonstrated transient cortical hypoperfusion in TGA patients with concomitant subcortical hypoperfusion only present in those patients whose amnesias were fully expressed during SPECT imaging.[15] Recent neuroimaging data have shown that the level of detection of lesions with diffusion-weighted magnetic resonance imaging (MRI) in TGA is a threshold phenomen dependent on the timing of imaging.[20]

In our current perfusion CT study, we were also able to detect cortical hypoperfusion in the frontal lobes, with involvement of the subcortical regions in patients during an amnestic state. The most important finding of the current study is the significantly lower CBF in the frontal grey matter. When analyzing left-right differences a longer duration of PTA was predominantly

associated with decreased CBF in the right hemisphere. This latter finding thus appears to be consistent with functional MRI studies of working memory that described a functional relationship with right frontal activity. [21] When a patient exhibits PTA, functional MRI shows a dysfunction in working memory and hence decreased activity could be expected in the acute phase. Memory is not localised to a single center in the brain but is subserved by a distributed network, including the frontal cortices. [22-27] The prefrontal cortices in particular appear to play an important role in explicit memory retrieval. [22,28,29] Local decreases in perfusion, which are indicators for local neuronal activity, may in this respect reflect functional deprivation due to a lesion in remote areas of such a network. [30] This might also explain the coherence between significantly decreased CBF in the frontal grey matter and caudate nucleus in our patient group.

One of the most intriguing aspects of PTA is the resolution of the amnestic state. Reabsorption of oedema may account for recovery of function in some cases, but to explain the tremendous variation in the duration of PTA, other reversible mechanisms must be operative. The concept of 'diaschisis', introduced as the cerebral variant of spinal shock, refers to the disruption of intact neuronal systems by localised lesions in distant but associated neurons or their connections and may play an important role in PTA. [1,31,32] The origin of this functional disruption is not well understood although a role for acetylcholine has been suggested. [1,33-35] We postulate that the involvement of the frontal cortices in memory retrieval and the principle of diaschisis provide an explanation for the significant decreased CBF in the frontal grey matter and the caudate nucleus in our PTA-group.

It should be noticed that the differences in CBF between the PTA-group and the post-PTA-group were relatively small compared to the ischemic values described in studies of patients with severe TBI [36] or cerebral ischemic stroke. [37] The differences, however, were significant, and might reflect impaired functioning caused by more subtle local damage or reduced network functioning caused by more subtle damage in remote areas. [30] Furthermore, in an earlier study we found decreased cerebral perfusion in mild TBI patients to be of prognostic value while in none of the patients ischemic levels were reached. [11]

Although it has been possible to study the amnestic state with perfusion CT, some limitations of our study have to be mentioned. The reversibility of the amnestic state was not studied by serial measurements in the same patient. The main reason for not performing repeated perfusion CT scans was the additional radiation exposure in a category of patients that are in general directly discharged from the hospital. Another issue is whether the time point of scanning post injury was a confounding factor with regard to the perceived CBF differences we found. However, no significant relationship between time of scanning and CBF differences was found. In addition, patients with an increased duration of PTA showed a larger decrease in CBF, which is an argument against the assumption that lower CBF occurs in the early hours after injury with subsequent improvement over time, as seen in severe TBI. [36]

One could argue that the injuries in our patient group were not severely enough to induce

decreases in CBF that reached ischemic levels, and thus only reflected temporarily dysfunction instead of structural damage. The non-contrast CT scan on admission showed no abnormalities whereas CT scans of the severe TBI all demonstrated abnormalities.[36] For future studies, it would be interesting to compare the perfusion CT results with MRI studies using susceptibility weighted imaging (SWI) and diffuse tensor imaging (DTI)-weighted sequences, to detect ischemic or axonal abnormalities. With regard to the absence of perfusion changes in the temporal cortex, it should be considered that partial volume effects from the skull may influence measurements of the basal temporal lobes. Further, the quantitative determination of distinct sub-profiles of memory impairment in the acute phase was not feasible, because elaborate neuropsychological tests could not be applied due to the relatively short duration of PTA. Hence, our results should be clarified by future neuropsychological examinations concerning residual memory impairment. Notwithstanding the acknowledged limitations, this study uniquely demonstrated regional changes in cerebral hemodynamics in patients that are actually suffering from PTA. Significant cortical and subcortical cerebral perfusion abnormalities were revealed in the prefrontal cortex and the interconnected caudate nuclei. Further studies should be done to explore the relationships between these hemodynamic changes in the acute phase after TBI with results of MRI studies and neuropsychological tests concerning long-term outcomes.

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Chapter

5

GFAP and S100B in the acute phase of mild traumatic brain injury

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ABSTRACT

The biomarkers Glial Fibrillary Acid Protein (GFAP) and S100B are increasingly used as prognostic tools in severe traumatic brain injury (TBI). Data for mild TBI are scarce. This study aims to analyse the predictive value of GFAP and S100B for outcome in mild TBI and the relation with imaging.

In 94 patients biomarkers were determined directly after admission. Collected data included injury severity, patient characteristics, admission computed tomography (CT) and magnetic resonance imaging (MRI) 3 months post injury. Six months after injury outcome was determined with extended Glasgow Outcome Scale (GOSE) and return to work (RTW).

Mean GFAP was 0.25 μg/L (SD 1.08) and S100B 0.54 μg/L (SD 1.18). In 63% GFAP was not discernable. GFAP was increased in patients with an abnormal CT (1.20 μg/L, SD 2.65) compared to normal CT (0.05 μg/L, SD 0.17, P = 0.02). Also in patients with axonal injury on MRI, GFAP was higher (0.65 μg/L (SD 0.91) vs. 0.07 μg/L (SD 0.2), P = 0.043). GFAP was increased in patients with incomplete RTW compared to complete RTW (0.69 μg/L (SD 2.11) vs. 0.12 μg/L (SD 0.38), P = 0.034). S100B was not related to outcome or imaging studies. In multivariate analysis GFAP was not predictive for outcome determined by GOSE and RTW.

A relation between GFAP with imaging studies and outcome (determined by RTW) was found in contrast to S100B. As the positive predictive value of GFAP is limited in this category of TBI patients, this biomarker is not suitable for prediction of individual patient outcome.

INTRODUCTION

Accurate determination of the neurological prognosis after traumatic brain injury (TBI) is of great importance in order to institute early rehabilitation. After mild TBI, most of the patients recover within weeks to months without specific therapy. However, a subgroup continues to experience disabling symptoms that interfere with their return to work or resumption of social activities. [1-5] In the acute phase after injury, computed tomography (CT) is the first choice for detection of brain injury with estimated sensitivity of 63-75% for detection of abnormalities. [6,7] However, approximately 20% of the patients who sustained mild TBI without abnormalities on the admission non-contrast CT experience problems with resuming work. [7] In addition to imaging studies and patient characteristics, biomarkers might provide information to determine injury severity and prognosis. Most commonly determined biomarker is S100B, a Ca-binding protein found in astroglial cells. Glial Fibrillary Acid Protein (GFAP) is found in glial cells in grey and white matter areas of the central nervous system. [8,9] It is a monomeric intermediate filament protein that represents the major part of the astroglial cytoskeleton [10] and is a highly specific marker for central nervous system pathophysiology. [11,12] In studies concerning severe TBI patients, the relation between injury severity and serum GFAP has been investigated. Levels of GFAP are related to the severity of brain injury and outcome. [12-14] In severe TBI with multiple traumas, S100B was related to brain injury but also elevated in extracranial injuries. [15,16] Especially the negative predictive power of S100B has been underlined; normal levels on admission are associated with good outcome. To date no studies are available examining the prognostic value of GFAP in mild TBI. [17]

The purpose of this study is to examine the prognostic value of serum GFAP in mild TBI patients in comparison to the more frequently used biomarker S100B. Furthermore, the relation with imaging studies and GFAP will be determined.

METHODS

Patients

Between May 2005 and June 2007, consecutive patients admitted with acute TBI were prospectively identified for enrolment in this study. Inclusion criteria were (1) age 18 to 65 years, (2) mild TBI defined as an initial GCS from 13 to 15 and (3) presence of posttraumatic amnesia (PTA). Patients with a history of neurological or psychiatric disease, mental retardation, addiction to alcohol or drugs or inability for long-term follow-up were excluded. A written informed consent was obtained from patients, family or next of kin if patients were unable or inadequate to provide consent.

Standard Protocols Approvals, Registrations and Patient Consents

The study was approved by the Medical Ethical Committee (METC) of the University Medical Center Groningen.

Serum markers

Blood samples were taken after admission at the Emergency Department. After centrifugation (10 minutes at 4000 rpm) serum samples were stored at -20 °C until determination of GFAP and S100B. Serum samples were stored at -80 °C for long-term storage. Serum GFAP levels were measured twice for each sample using a commercial enzyme-linked immunosorbent assay (ELISA; Biovendor GmbH, Heidelberg, Germany). The detection limit for GFAP was 0.045 ng/ml. Serum levels of S100B were measured twice for each sample using two commercial available ELISA assays (Biovendor and DiaSorin, Saluggia, Italy, EU). The detection limit of S100B was 0.005 ug/L. The respectively intra-assay coefficients were 1 % for GFAP and 2.95 % for S100B. Standard curves for GFAP and S100B were constructed by plotting the absorbance values against concentrations of standards. Standardised curves were assessed using non-linear regression analyse from SigmaPlot. Concentrations of unknown samples were determined using these standard curves (not shown).

Imaging

In all patients a non-contrast CT of the brain (Siemens Sensation 64) was performed on admission. The CT scans were reconstructed into 5 and 2 mm thick adjacent slices through the whole brain, matrix size of 512 x 512. Evaluation of CT scans was done according to the Marshall classification.18 Furthermore, the presence of contusions was noted with sub-classification in the frontal, temporal, parietal and occipital or brainstem/cerebellar region. At three months follow-up an MRI scan was obtained (Siemens Sonata, 1.5T) with the following sequences: transversal T1-weighted spin echo (SE), transversal and coronal T2*-weighted gradient-recalled-echo (GRE; all with 6mm slice thickness) and coronal T2-weighted turbo SE (4mm slice

thickness). The images were reviewed by an experienced neuroradiologist (L.R.) without knowledge of outcome of patients.

Outcome

Six months after injury the outcome was determined with the extended Glasgow Outcome Scale (GOSE). 19 The GOSE comprises eight outcome categories: 8 = good recovery; 7 = good recovery with minor physical or mental deficits; 6 = moderate disability, return to previous work with some adjustments; 5 = work at a lower level of performance; 4 = severe disability, for some activities dependent on others; 3 = severe disability, completely dependent; 2 = vegetative state; and 1 = death. Outcome was dichotomised as optimal (GOSE = 8) and suboptimal (GOSE < 8). Return to work (RTW) was scored as 0 = previous work/study completely resumed; 1 = work/study part-time resumed, or with lower demands; 2 = previous work not resumed but working on a lower level; or 3 = not working. RTW was dichotomised in complete RTW (RTW = 0) and incomplete RTW (RTW ≥ 1).

A symptom checklist containing 19 symptoms evaluated complaints that are frequently reported after trauma.

Statistical analysis

All statistical analyses were done using SPSS (Statistical Package for the Social Sciences) version 18.0 (SPSS, Chicago, IL). To compare biomarker levels between groups mean levels were presented, no predefined cutoff level was used. Comparison between groups was done with Mann-Whitney tests in case of 2 groups and Kruskal-Wallis test in 3 or more groups. For normal distributed variables analysis of variance (ANOVA) was used. A Bonferroni correction was applied, where appropriate. The sensitivity, specificity, and negative predictive value of dichotomised GFAP were determined. Logistic regression analysis was applied for calculating the predictive value of dichotomised outcome measures GOSE and RTW. Statistical significance was defined as P-value < 0.05.

RESULTS

Patient characteristics

A total of 94 patients fulfilled the inclusion criteria. Patient characteristics are displayed in Table 1. Blood samples for GFAP and S100B measurements were obtained on average 2.4 hours (SD 2.1) after injury. In a total 16 patients, fractures of the extremities (12), ribs (6) and spinal column (5) were present. In addition, in 24 patients fractures of the skull, skull base, facial bones, or a combination of these were present. A total of 59% of accidents were traffic-related, with car/motorcycle (24%) and bicycle (29%) most commonly involved.

Table 1. Patient characteristics.

		GCS 13-15 (N = 94)#	GCS 13 (N = 11)	GCS 14 (N = 58)	GCS 15 (N = 25)
Age, mean (SD)		34.3 (13.9)	31.3 (13.6)	32.8 (13.6)	39.1 (14.0)
PTA, hours, mean (SD)		12.8 (25.9)	28.8 (33.7)	13.8 (26.9)	3.9 (15.2)
CT abnormalities (%)		20	73	17	4
MRI axonal injury (%)		63	21	20	
(N = abnormal/total MRIs)			(5/8)	(7/33)	(2/9)
GOSE(%)	5	3	-	4	-
	6	19	30	23	4
	7	32	40	32	24
	8	46	30	41	72
Complete RTW (%)		76	70	71	88

Abbreviations: CT = computed tomography, GCS = Glasgow Coma Score, GOSE = extended Glasgow Outcome Scale, MRI = magnetic resonance imaging, PTA = posttraumatic amnesia, RTW = return to work.
missing outcome in 3 patients.

GFAP and S100B and severity of injury

The mean concentration of GFAP in the total patient group was 0.25 μg/L (SD 1.08). In 59 patients (63%) no GFAP was detectable. The mean concentration of S100B was 0.54 μg/L (SD 1.18). When comparing patients with various GCS no difference for mean GFAP and S100B levels between groups was found.

GFAP and S100B and non-contrast CT

In 20% of patients CT abnormalities according to Marshall classification were present. In those with an abnormal CT (N = 19) the GFAP concentration was higher compared to those with a normal CT (N = 75) with 1.20 μg/L (SD 2.65) vs. 0.05 μg/L (SD 0.17), P = 0.02. For S100B no difference was found between patients with an abnormal CT and a normal CT. The presence of

focal contusions correlated with GFAP, R = 0.63 (P < 0.01). In those patients with one or more contusions the GFAP was increased (1.70 μg/L, SD 2.82) compared to those without contusions (0.05 μg/L, SD 0.19, P = 0.03).

GFAP and S100B and MRI

In 50 (53%) patients a MRI scan was performed, with a mean time after injury of 111 days (SD 68). Axonal injuries detected with T2*-weighted GRE-sequences correlated with GFAP, R= 0.46 (P < 0.01). In patients with axonal injury (N = 14) GFAP was higher (0.65 μg/L, SD 0.91) compared to patients (N = 36) without axonal injury (0.07 μg/L, SD 0.22, P = 0.043). No relation between MRI and S100B levels was found. Comparison of groups with respect to CT and MRI abnormalities (Figure 1) showed different (P = 0.01) concentrations of GFAP between groups, with the highest concentration of GFAP in those with both CT and MRI abnormalities. GFAP showed a high negative predictive value for imaging (Table 2).

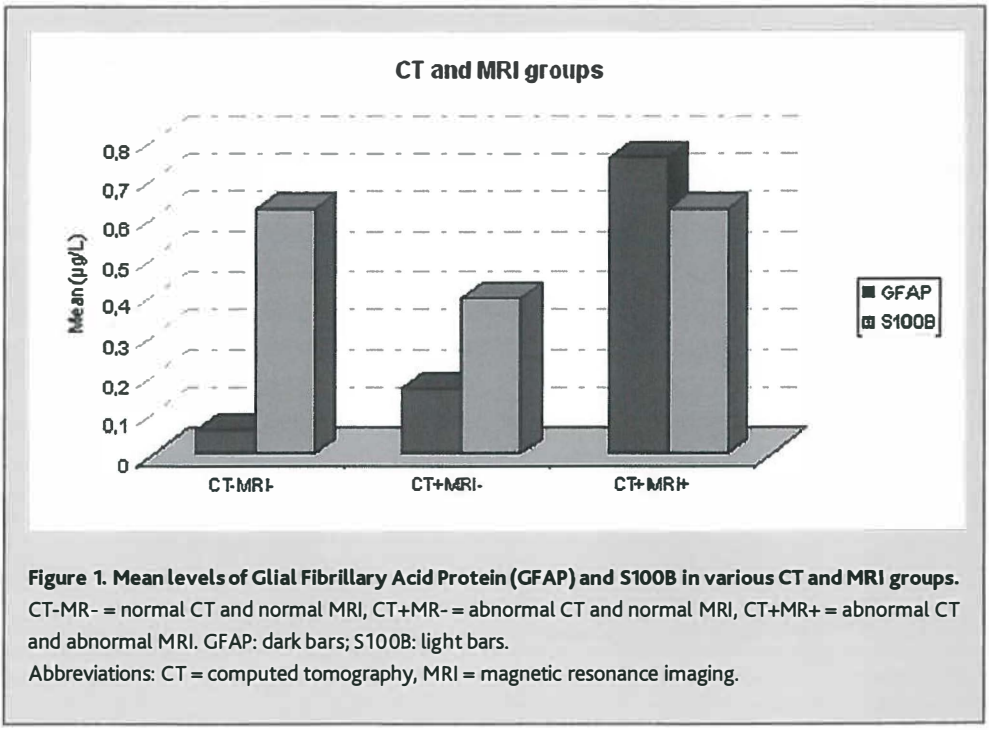

Figure 1. Mean levels of Glial Fibrillary Acid Protein (GFAP) and S100B in various CT and MRI groups.
CT-MR- = normal CT and normal MRI, CT+MR- = abnormal CT and normal MRI, CT+MR+ = abnormal CT and abnormal MRI. GFAP: dark bars; S100B: light bars.
Abbreviations: CT = computed tomography, MRI = magnetic resonance imaging.

Table 2. Sensitivity, specificity and predictive values of Glial Fibrillary Acid Protein (GFAP) in relation to magnetic resonance imaging (MRI), return to work (RTW) and extended Glasgow Outcome Scale (GOSE).

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
MRI	0.62	0.45	0.47	0.62
RTW	0.65	0.72	0.36	0.29
GOSE	0.50	0.82	0.67	0.56

GFAP and S100B and outcome

Six months outcome was favourable (GOSE 7 and 8) in 78% of patients with 76% returning to previous work. When dichotomised for RTW, GFAP was higher (Figure 2) in those patients with incomplete RTW (0.69 μg/L, SD 2.11) compared to those with complete RTW (0.12 μg/L, SD 0.38, P = 0.034). The amount of complaints correlated with GFAP (R = 0.26, P < 0.05) although no specific complaints could be discerned. No relation of S100B with complaints, GOSE or RTW was demonstrated. GFAP in patients with optimal outcome according to the GOSE (0.45 μg/L, SD 1.49) was not different from patients with suboptimal outcome (0.06 μg/L, SD 0.21, P = 0.096). All 4 patients with a GFAP level above 1.5 μg/L showed suboptimal outcome according to the GOSE with abnormal admission CT.

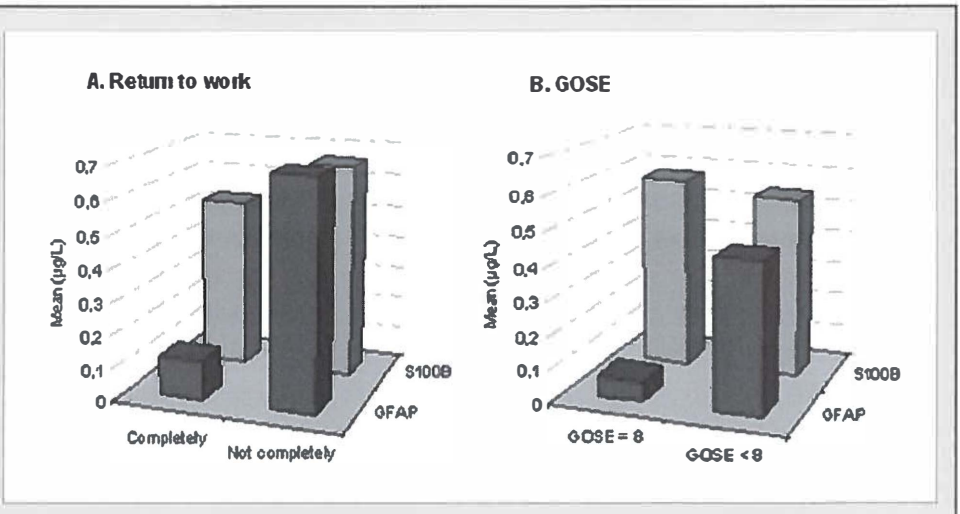

Figure 2. Mean levels of Glial Fibrillary Acid Protein (GFAP) and S100B related to resumption of work (A) and extended Glasgow Outcome Scale (GOSE, B).
GOSE = 8 represents optimal outcome and GOSE < 8 suboptimal outcome.
GFAP: dark bars; S100B: light bars.

In univariate regression analysis GFAP was predictive for outcome determined by the GOSE (0.27, 95% CI 0.059-1.19, P = 0.048) in addition to GCS (2.80, 95% CI 1.30-6.07, P = 0.009). Age, PTA and Marshall score were not significant. In multivariate regression analysis the predictive value of GFAP for outcome was not significant. S100B levels were not found to be predictive for outcome in regression analysis.

DISCUSSION

We examined admission values of serum GFAP and S100B in relation to CT and MRI and evaluated the predictive value regarding outcome in patients with mild TBI. To date, no earlier studies are available examining the prognostic value of GFAP in mild TBI. In this study, GFAP was found to be related to imaging and outcome as defined by return to work whereas S100B was found not to be of prognostic value in this patient category.

In TBI, GFAP is regarded as a more specific indicator of brain damage whereas S100B also is released by extracranial injuries. In severe TBI, GFAP levels are increased when mass lesions and raised intracranial pressure are present. [13,20] In severe TBI with multiple injuries, S100B is related to brain injury but also to the presence of extracranial injuries. [15,16] In isolated TBI serum GFAP was found to be a more useful marker of brain damage than S100B or NSE. [21] In this study of mild TBI, GFAP and S100B were not related to severity of injury, as opposed to findings in severe TBI. The reason for this finding could be due to the fact that in the mild TBI category less variation in GCS is seen as it contains also patients with nearly normal GCS.

Imaging studies in the acute phase, in addition to the GCS, could also be regarded as a marker for severity of brain injury. In severe TBI, the presence of mass lesions is associated with elevated serum GFAP, [20] and a significant relation between GFAP and outcome has been established. [14,20,22] In the current study, GFAP was higher in patients with an abnormal admission CT compared to patients with a normal CT. As MRI studies are more increasingly applied to determine axonal injury that is related to outcome, [23] the predictive value of GFAP for this imaging modality was explored. We found a relation between levels of GFAP and the presence of MRI abnormalities. This indicates that GFAP as a biomarker in the acute phase is related to axonal injury that is still present several months after injury. However, the positive predictive value of GFAP for MRI abnormalities is low, presumably because most patients in this study did have a normal MRI.

When regarding outcome, no difference in absolute GFAP levels could be discerned between those with optimal and suboptimal outcome as determined by the GOSE. However, when resumption of work was taken into account, GFAP was significantly higher in patients who were not able to resume work on previous level. An explanation for this missing relation with GOSE, in contrast to studies with severe TBI, could be the ceiling effect of the GOSE, as three in four patients showed outcome in the highest outcome scales defined by favourable outcome in the GOSE. Presumably RTW represents more accurate the actual daily functioning of patients than the GOSE, as this scale is also related to the complaints of patients.

In this study GFAP is compared with S100B, a more commonly used biomarker in trauma patients. High levels of S100B are associated with reduced work resumption, neuropsychological impairments and CT abnormalities. [24,25,26] Especially the negative predictive value of S100B in mild TBI has been underlined; normal levels on admission are associated with good outcome. [27] The finding that GFAP appears a more sensitive marker than S100B for outcome in our study

might be related to the extent of extracranial injuries in our study. These injuries are known to be related to increased S100B, [15] limiting the predictive value of S100B. Furthermore, the current study comprises more patients with GCS with 13 and 14 in comparison with these aforementioned studies that revealed a relation of S100B and outcome. In 63% of patients no GFAP was discernable, questioning the predictive value of this specific biomarker for mild TBI. The GFAP levels in our study were determined within 3 hours after injury, which is regarded as a reliable interval after trauma. If measured within 6 hours after trauma GFAP levels were found to be reliable predictor of outcome. [28] The negative predictive value of GFAP for outcome was moderate as 19% of patients with a nondetectable GFAP moderate disability according to the GOSE and 21% did not resume previous work. Regarding specific cut-off values, in all patients with GCS 15 the GFAP levels were below 0.5 μg/L. In severe TBI a cut-off value of 1.5 μg/L is used for prediction of mortality. [29] In the present study, all patients with a value above this limit showed suboptimal outcome, although no patients died. In univariate analysis GFAP was found to be predictive for outcome but this effect was lost in multivariate analysis, suggesting that GFAP is not an independent factor to determine outcome. Therefore, the relation between injury severity and ultimate outcome in this patient category is more complex than solely defined by these biomarkers on admission and 6-month outcome.

A limitation of the current study is that the levels of biomarkers were not compared with healthy control subjects. However, in this mild TBI group, we intended to determine the relation between detected levels and several outcome parameters. As GFAP is a brain-specific marker we assume that by comparing groups with detectable versus nondetectable GFAP, the results concerning the relation with imaging and outcome still provides valuable information for the application of this relative new biomarker.

Our data show a relation of GFAP and brain injury severity as determined with CT and MRI. GFAP is not necessarily related to outcome, as determined by GOSE and RTW. As the category of mild TBI also includes less sever injuries with nondiscernible GFAP, the predictive value is limited and this biomarker appears not useful in making clinical decisions or for prediction of outcome in this patient group.

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Chapter

6

Pathophysiological concepts in mild traumatic brain injury: diffusion tensor imaging related to acute perfusion CT imaging

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Submitted

ABSTRACT

A subgroup of mild traumatic brain injury (TBI) patients experiences residual symptoms interfering with return to work. The substrate of the suboptimal outcome in these patients raises much debate. We performed diffusion tensor imaging analysis during follow-up in eighteen patients who obtained perfusion CT imaging in the acute phase of injury. A trend was observed for a decreased fractional anisotropy (FA) in widespread bilateral frontal white matter areas with increased mean diffusivity (MD) in the parieto-temporal regions. FA correlated significantly ($P < 0.05$) with cerebral blood volume (CBV) in the parieto-temporal and occipital regions. The pathophysiological concept of these findings is outlined.

INTRODUCTION

A subgroup of patients with mild traumatic brain injury (TBI) continues to experience disabling symptoms that interfere with their return to work or resumption of social activities. [1] These symptoms not only cause a personal but also a socioeconomical burden, since it often affects young patients in their twenties and thirties with full occupational status. In Europe TBI accounts for the highest number of total years lived with disability from trauma and belongs to the top three of hospital costs per inhabitant. [2] It is of paramount importance to understand which mild TBI patients will develop cognitive disability in order to institute early rehabilitation. With imaging both axonal injury and hemodynamic changes in mild TBI have been demonstrated. [3] In an earlier study we found frontal hypoperfusion in the acute phase of mild TBI patients with a normal conventional computed tomography (CT). [4] Diffuse axonal injury (DAI), a major pathological substrate of TBI, can be visualised with diffusion tensor imaging (DTI), also in the mild TBI category. The precise relation between hemodynamic changes in the acute phase and axonal injury remains speculative.

The purpose of this study was to examine the relation between the DTI during follow-up and perfusion CT in the acute phase after mild TBI, in order to explore possible common pathophysiological mechanisms.

METHODS

Participants

Patients admitted with acute TBI were prospectively identified for enrolment in this study. Inclusion criteria were (1) age 18 to 65 years, (2) mild TBI defined as an initial GCS from 13 to 15 and (3) posttraumatic amnesia (PTA). Patients obtained a cerebral non-contrast CT and a perfusion CT on admission. This patient cohort was described earlier, [4] in this part of the study only patients were analysed when DTI was obtained during follow-up. Exclusion criteria comprised prior neurological or psychiatric disease, mental retardation, addiction to alcohol or drugs or inability for follow-up. Pregnancy, diabetes, nephropathy, presence of MRI-incompatible materials and contrast allergy were additional exclusion criteria. A written informed consent was obtained from patients, family or next of kin. Nineteen healthy volunteers (11 men, 8 women; mean age 38.7 years (SD 10.4) underwent the same magnetic resonance imaging (MRI) protocol. The study was approved by the Medical Ethical Committee of the University Medical Center Groningen.

Imaging

Perfusion CT imaging

CT scans were performed on a Siemens Somatom Sensation 64-row CT scanner (Siemens Medical Systems, Erlangen, Germany). Two adjacent 14.4 mm thick slabs were positioned at the level of the third ventricle and at the level of the centrum semiovale. A 40-ml volume of a non-ionic iodinated contrast agent (Visipaque 270 mg/mL) was power-injected, followed by a saline chase. After 5s delay, a dynamic scan was initiated with the following parameters: 80 kV, 100 mA, and 1 s per rotation for a duration of 46 s. Post-processing was performed by a neuroradiologist (L.R.) using TeraRecon perfusion software (TeraRecon Inc., San Mateo, CA). A Gamma variate fitting curve was applied. The deconvolution algorithm produced two sets of colored parameter maps for cerebral blood flow (CBF), mean transit time (MTT) and cerebral blood volume (CBV). By using a preset of regions of interest (ROIs) quantitative values for CBF, MTT and CBV were generated in the frontal, temporal and occipital white and grey matter.

Diffusion Tensor Imaging

Diffusion-weighted (DW) images were acquired using a PGSE EPI sequence (TR/TE = 4900/91 ms; NEX = 3) on a 1.5T Siemens Sonata (8-channel head coil) along 12 noncollinear directions (maximum gradient strength 40 mT/m; b-value 1000; matrix 128 x 128; FOV 230 x 230 mm; no gap; reconstructed voxel size 0.9 x 0.9 x 5 mm^3; 31 transverse slices). One image without diffusion gradients (b0) was also acquired. DW images were corrected for motion and eddy-currents using FSL. [5,6] After b0 skull-stripping, FSL Fdt was used to perform diffusion tensor estimation and to calculate fractional anisotropy (FA) and mean diffusivity (MD) in each brain voxel. The resulting images were used to assess between-groups differences using Tract-Based

Spatial Statistics (TBSS).[7] TBSS focuses on the voxels of the white matter skeleton approximating the center of the main fiber tracts, obtained from the group mean FA image after nonlinear registration of each subject's FA map into a common space. No spatial smoothing is required. This approach increases the statistical power and prevents the results to be driven by partial volume effects or confounding morphological differences (such as ventricles enlargement).

Statistical analysis

Between-group differences in white matter integrity, quantified by FA and MD values, were estimated with a general linear model (GLM) with different predictors for groups. In the patients group, linear regression was used to estimate the association between perfusion CT scores and FA/MD values. In both analyses, age and sex were used as covariates of no interest. Inference was carried on using nonparametric permutation testing[8] (5000 permutations) and corrected for multiple comparisons using threshold-free cluster enhancement.[9]

RESULTS

Patient characteristics

Eighteen patients fulfilled the inclusion criteria. Patient characteristics are displayed in Table 1. The mean time between injury and perfusion CT imaging was 3.6 hours (SD 1.3). The mean time between injury and DTI was 160 days (SD 109).

Table 1. Patient characteristics.

Patient characteristics (N = 18)		
Mean age in years, mean (SD)		38.0 (14.4)
Male		15 (84)
Traffic accidents		7 (39)
GCS, mean (SD)		14.3 (0.7)
	15	7 (39)
	14	9 (50)
	13	2 (11)
Duration PTA in hours, mean (SD)		5.75(11.9)
GOSE, mean (SD)		7.17 (0.86)
	8	8 (44)
	7	5 (28)
	6	5 (28)
Return to work	Complete	13 (72)
	Parttime	5 (28)

Abbreviations: GCS = Glasgow Coma Score, PTA = posttraumatic amnesia, GOSE = extended Glasgow Outcome Scale. Values are number (%) unless noted otherwise.

Patients versus healthy control subjects

There was a trend towards a decreased FA in the patient group ($P < 0.08$) in widespread bilateral white matter areas in the frontal regions, including the inferior fronto-occipital fasciculus as well as the white matter region underneath the right hemisphere precuneus (Figure 1). The MD was, although not significantly, increased in the parieto-temporal regions ($P < 0.07$) in the patient group compared to the healthy control subjects.

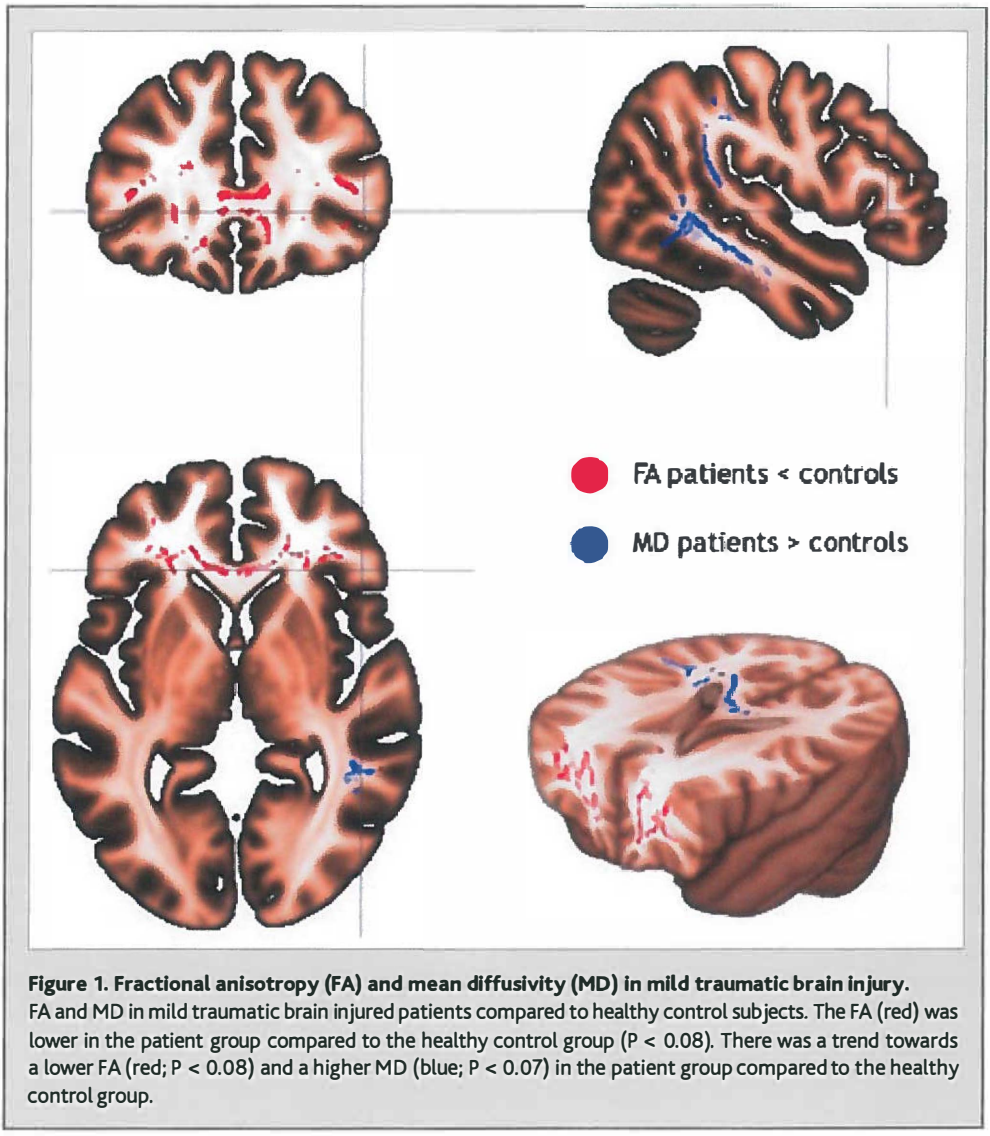

Figure 1. Fractional anisotropy (FA) and mean diffusivity (MD) in mild traumatic brain injury. FA and MD in mild traumatic brain injured patients compared to healthy control subjects. The FA (red) was lower in the patient group compared to the healthy control group ($P < 0.08$). There was a trend towards a lower FA (red; $P < 0.08$) and a higher MD (blue; $P < 0.07$) in the patient group compared to the healthy control group.

Relation with perfusion CT imaging

In all patients, perfusion CT scanning was completed without complications, no adverse reactions to the contrast material occurred. There was a significant ($P < 0.05$) positive correlation between CBV in white and grey matter areas in the parieto-temporal and occipital lobes and FA. Hence, a lower CBV was correlated with a lower FA (Figure 2). No negative correlations could be discerned.

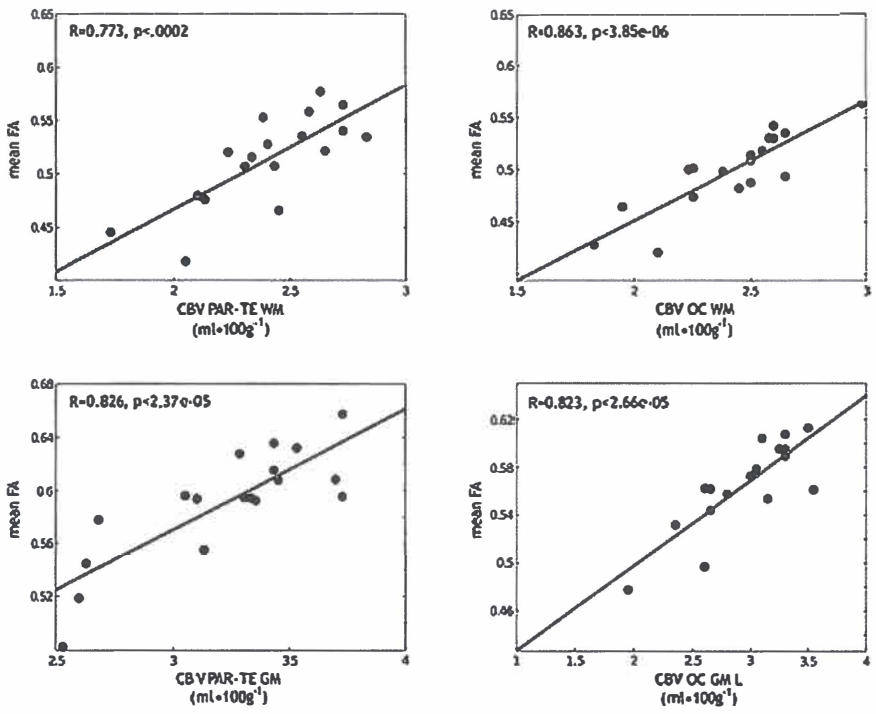

Figure 2. Fractional anisotropy (FA) in relation to cerebral blood volume (CBV) in mild traumatic brain injury.
Significant ($P < 0.05$) correlations between FA and CBV in different cerebral areas in mild traumatic brain injured patients.
Abbreviations: PAR-TE = parieto-temporal, OC = occipital, WM = white matter, GM = grey matter, L = only on the left side.

DISCUSSION

This is the first study, that showed a relation between DTI and cerebral perfusion in mild TBI. In patients with mild TBI and normal conventional imaging a trend was observed with DTI abnormalities in the chronic phase compared with healthy control subjects. More importantly, these DTI findings are related to hemodynamic abnormalities assessed with perfusion CT imaging in the acute phase of injury.

A challenging question is how to interpret the relation between these aforementioned findings. In the acute phase after injury, hemodynamic changes are found in mild TBI. [4] Furthermore, several DTI studies identified white matter abnormalities in patients with mild TBI. [10-16] In general a decreased FA and an increased MD is seen in the chronic phase after injury, [10,13,15,16] in accordance with our study. The most likely cause of these white matter changes is DAI. The precise sequence of events over time regarding this axonal injury remains poorly understood, especially in relation to the hemodynamic changes in acute phase after injury. Classically, primary brain injury occurs at the moment of impact, with DAI as most important mechanism, also in mild TBI. [17] Secondary brain injury evolves in the hours after injury and mainly comprises ischemia, considered as a consequence of primary brain injury. Interestingly, Ueda and colleagues demonstrated in rat models that axonal damage is associated with vascular abnormalities in the early stage after injury. They suggested that injury forces also might damage the perivascular nerve networks, thereby contributing to the hemodynamic abnormalities. [18] Hence, the white matter abnormalities we observed in the present study might be secondary to cerebral hemodynamic disturbances or are part of the same pathophysiological mechanism in the acute phase. For example, DAI results in impaired axonal transport and swelling compromising small capillaries that could further contribute to hemodynamic changes. The axon will undergo Wallerian degeneration of the axon and the consecutive structural reorganization can be reflected in changes in FA and MD.

As white matter integrity is related to the brain network function, it would be intriguing to explore whether the findings of the present study are related to changes in brain connectivity as measured with functional MRI (fMRI). [19,20] In mild TBI patients, Mayer and colleagues demonstrated in the subacute phase an altered functional connectivity within the default-mode network, with an elevated FA in white-matter tracts between the primary nodes of this connectivity network. [21] Furthermore, an association is found between neuropsychological impairment and diffusivity changes in the long association white matter tracts. [22] These anatomical findings are grossly in accordance with the present study, which also revealed the major DTI abnormalities in the frontal and parieto-temporal areas.

In summary, despite limitatons such as the small sample size that limits overall generalisability of the results, with this study challenging information is added to the discussion of the pathophysiological concept of mild TBI.

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Chapter

7

Cerebral perfusion and neuropsychological follow-up in mild traumatic brain injury: acute versus chronic disturbances?

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ABSTRACT

In a subgroup of patients with mild traumatic brain injury (TBI) residual symptoms interfering with outcome and return to work are found. With neuropsychological assessment cognitive deficits can be demonstrated although the pathophysiological underpinnings of these cognitive deficits are not fully understood. As the admission computed tomography (CT) often is normal, perfusion CT imaging may be useful as indicator of brain dysfunction in the acute phase after injury in these patients.

In the present study, directly after admission perfusion CT imaging was done in mild TBI patients with follow-up neuropsychological assessment in those with complaints and a normal non-contrast CT. Neuropsychological tests comprised the 15 Words test Immediate Recall, Trailmaking test part B, Zoo Map test and the FEEST, which were dichotomised in to normal and abnormal. Perfusion CT results of patients with normal neuropsychological test scores were compared to those with abnormal test scores.

In total eighteen patients were included. Those with an abnormal score on the Zoo Map test had a significant lower CBV in the right frontal and the bilateral parieto-temporal white matter. Patients with an abnormal score on the FEEST had a significant higher MTT in the bilateral parieto-temporal white matter and a significant decreased CBF in the left parieto-temporal grey matter. No significant relation between the perfusion CT parameters and the 15 Words test and the Trailmaking test part B was present.

In conclusion, impaired prefrontal regulated functions of executive function and social cognition assessed with neuropsychological tests during follow-up were related to differences in cerebral perfusion at admission in mild TBI. The pathophysiological concept of these findings is discussed.

INTRODUCTION

The majority of the patients with mild traumatic brain injury (TBI) recover within weeks to months without specific therapy. However, a subgroup continues to experience disabling symptoms that interfere with their return to work or resumption of social activities. [1-5] These symptoms comprise headaches, dizziness, memory problems and difficulties with learning new tasks. [6]

There is no consensus in the literature regarding neuropsychological deficits in mild TBI. Most studies have suggested that cognitive deficits occur shortly after injury with the impairment usually dissipating at 1-3 months post injury. [7-13] Still other, often smaller, studies have shown that persistent impairment can be present in patients with mild TBI. [14-19] Impairments in a range of cognitive domains at long-term follow-up have been documented after mild TBI, [20] with most deficits involving attention and concentration, [15,17,21] memory, [7,12,14,18,19] speed of information processing, [7] verbal fluency, [17] and executive functions. [7,11] Conventional computed tomography (CT) characteristics are not a sufficient predictor of outcome in this patient category knowing that approximately 20% of the patients with mild to moderate TBI with a normal non-contrast CT experience problems with resuming work. [22] More recent neuroimaging techniques may improve knowledge in the pathophysiology of mild TBI, increase the sensitivity for detecting abnormalities and, hence, allow the development of better prognostic indicators.

Hemodynamic imaging has gained insight in the pathophysiological mechanisms of TBI although, up till now, only a small number of hemodynamic imaging studies have been performed in the acute phase of mild TBI, in particular single photon emission CT (SPECT), [23-25] Xenon-CT, [26] and perfusion CT. [27] These studies did reveal cerebral perfusion abnormalities in patients with a normal conventional CT scan. In addition, Audenaert and colleagues [25] assessed a good topographical accordance between SPECT abnormalities and neuropsychological testing in the acute phase, although they did not examine long-term neuropsychological outcome. Nevertheless, to date the precise relation of cerebral perfusion in the acute phase of injury with cognitive functioning during follow-up is unclear. Perfusion CT is an imaging modality using the dynamics of the distribution of intravenous contrast to determine cerebral perfusion in the brain, and can easily be performed in the emergency setting. In a previous study on mild TBI we found that perfusion CT abnormalities were predictive for the outcome according to the extended Glasgow Outcome Scale (GOSE). [27] For this reason we conducted the present study in which we aimed to determine whether brain dysfunction as indicated by perfusion CT imaging at admission is related to abnormal neuropsychological tests during follow-up in mild TBI patients with a normal conventional CT. More specifically, we would expect a relation between frontal and temporal cerebral hypoperfusion and neuropsychological deficits as these brain areas are strongly involved in higher cognitive functions regarding memory, attention, executive and social cognition.

METHODS

Participants

Between 2005 and 2007 consecutive patients admitted with acute TBI were prospectively identified for enrolment in this study. Inclusion criteria were (1) age 18 to 65 years, (2) mild TBI defined as an initial GCS from 13 to 15 and (3) posttraumatic amnesia (PTA). In the present study, only patients without intracranial abnormalities on the non-contrast CT were further analysed. A subgroup underwent neuropsychological testing during follow-up (on average 3.5 months post injury), because of posttraumatic complaints. Patients with a history of neurological (also previous TBI) or psychiatric disease, mental retardation, addiction to alcohol or drugs or inability to long-term follow-up were excluded. Pregnancy, a history of diabetes, nephropathy and contrast allergy were additional exclusion criteria. A written informed consent was obtained from patients, family or next of kin if patients were unable or inadequate to provide consent. The study was approved by the Medical Ethical Committee (METC) of the University Medical Center Groningen and was in compliance with the Helsinki Declaration.

Complaints

A checklist of complaints was filled out which contains symptoms that are frequently reported in the literature as part of the sequelae of TBI. This symptom checklist is comparable to the Head Injury Symptom Checklist (HISC) [28] with addition of symptoms not related to concussion. These items were meant to check an increased tendency to complain. To control for the base rates of complaints in the general population, subjects were also asked if they experienced any of the complaints before the injury, and if they did, whether these had stayed the same or had worsened since the injury. In addition, they were also asked to qualify their symptoms as occurring seldom or often. In this manner the total number of (posttraumatic) complaints and the severity of symptoms were recorded.

Perfusion CT imaging

The CT scans were made on a Siemens Somatom Sensation 64-row CT scanner (Siemens Medical Systems, Erlangen, Germany). First a standard non-contrast CT of the brain was performed, followed by a perfusion CT. In our patient group, the non-contrast CT scans were all evaluated by a radiologist on call. A central re-review was performed within a few days after trauma by an experienced neuroradiologist (L.R.). Two adjacent 14.4 mm thick slabs, perpendicular to the hard palate, were positioned at the level of the thalami, basal ganglia and third ventricle and at the level of the centrum semiovale and the lateral ventricles. A 40-ml volume of a non-ionic iodinated contrast agent (Visipaque 270 mg/mL) was power-injected at a rate of 5 ml/s, followed by a 20-ml saline chase. After 5s delay, a dynamic scan was initiated with the following parameters: 80 kV, 100 mA, and 1 s per rotation for a duration of 46 s. The estimated radiation

dose was acceptable to the standards of our Medical Ethical Committee. Post-processing was also performed by an experienced neuroradiologist (L.R.) using TeraRecon perfusion software (TeraRecon Inc., San Mateo, CA). A Gamma variate fitting curve was applied. The deconvolution algorithm produced two sets of colored parameter maps for cerebral blood flow (CBF), mean transit time (MTT) and cerebral blood volume (CBV). By using a digitally saved preset of regions of interest (ROIs) quantitative values for CBF, MTT and CBV were generated in the frontal, parieto-temporal and occipital white and grey matter on the two slabs. These two slabs were averaged and stratified for the regions and the three perfusion parameters. In this part of the study we only analysed the frontal and parieto-temporal ROIs.

Neuropsychological test measures

The test battery comprised cognitive tests for memory and attention, as well as for aspects of executive function and social cognition, conceived as prefrontal regulated functions. Patients performed the test battery in a single 2-hour test session. The order in which the tests were presented was randomly varied across the patients. All test scores were dichotomised into normal or abnormal, according to the available norm data or cut-off scores.

15 Words test (Dutch version of the Rey Auditory Verbal Learning test (RAVLT) [29]

The 15 Words test is a verbal memory test, of which the Immediate Recall (IR) test was used in this study. In this task a set of 15 unrelated words is presented to the subject, who is asked to reproduce immediately as many of the words as possible. This is repeated in 4 subsequent trials. The score (maximum 75) is a score of immediate recall from verbal memory. Based on the Dutch norm group T-scores were calculated and a T-score < 37 was categorised as abnormal.

Trailmaking test part B [30]

The Trailmaking test is a test for mental speed (part A) and switching attention (part B). Only part B was used; in this subtest the subject has to alternate between numbers and letters displayed on a sheet while connecting them with a pen in ascending order as quickly as possible. The dependent variable is the time (in seconds) to finish the test. Based on the Dutch norm group, T-scores were calculated and a T-score < 37 was categorised as abnormal.

Zoo Map test (BADS) [31]

The Zoo Map test is a subtest of the Behavioral Assessment of the Dysexecutive Syndrome (BADS) battery. Subjects are required to show how they would visit a series of designated locations on a map of a zoo while having to adhere to certain rules. This is a test measure for executive functioning in which the ability to formulate and implement a plan is assessed. This subtest was found to be sensitive to TBI related pathophysiology, [32] and has shown to have concurrent validity with other executive functioning measures. [33]

The maximum score is 16 and the minimum score can be lower than zero. Scores below 10 (which was 1 SD below the mean of a healthy control group) [34] were categorised as abnormal.

FEEST [35]

The FEEST (Facial Expression of Emotion-Stimuli and Tests) is a test for perception of emotional expressions on faces as a measure for social cognitive functioning. The test was found to be sensitive to TBI related frontal pathophysiology. [34] Sixty faces are shown and the expressions depicted are the primary emotions Fear, Disgust, Sadness or Surprise (10 of each). Stimuli are presented for 3 seconds after which the subject has to choose which emotion label best describes the emotion shown. The score ranges from 1-60. A score below the cut-off score, with age taken into account, was categorised as abnormal.

Outcome

At 6 months after injury the outcome was determined with two outcome measures: the extended Glasgow Outcome Scale (GOSE) [36] and return to work (RTW). The GOSE comprises eight outcome categories: 8 = good recovery; 7 = good recovery with minor physical or mental deficits; 6 = moderate disability, return to previous work with some adjustments; 5 = work at a lower level of performance; 4 = severe disability, for some activities dependent on others; 3 = severe disability, completely dependent; 2 = vegetative state and 1 = death. We dichotomised outcome as optimal (GOSE = 8) and suboptimal (GOSE < 8). RTW comprises four categories: 0 = previous work or study resumed; 1 = previous work or study resumed, but with lower demands or part-time; 2 = previous work or study not resumed, different work on a lower level; 3 = not working. We also dichotomised return to work as optimal if patients completely resumed their previous work or activities, and suboptimal if patients resumed their previous work on a part-time basis or lower level, or if they could not resume their previous work.

Statistical analysis

Statistical analysis concerning neuropsychological testing is performed using Statistical Package for the Social Sciences version 18.0. To test for differences in cerebral perfusion parameters (CBF, MTT and CBV) between those with normal and abnormal neuropsychological test results, analysis of variance (ANOVA) was used. These analyses were stratified by the three perfusion parameters and the anatomical regions in the frontal and parieto-temporal white and grey matter. Adjustment for age and gender was effectuated by using them as covariates in the analysis, as these parameters influence cerebral perfusion. ANOVA was also used to examine differences in complaints between those with normal and abnormal results on the four neuropsychological tests. In order to analyse the relation between dichotomised neuropsychological test data and dichotomised outcome data (GOSE and RTW) Chi-Square test was used. Statistical significance was defined as P-value < 0.05.

RESULTS

Patient characteristics

Eighteen patients were included in the analysis. Only 1 patient had missing values on two of the four tests. Patient characteristics are displayed in Table 1. The mean age of the patient group was 35.2 years (SD 14.3), with a majority of males (N = 13). Most (N = 14) injuries were traffic related and the majority (N = 14) of patients had a GCS of 14.

The mean time between injury and perfusion CT scanning was 3.8 hours (SD 1.7). In all patients, perfusion CT scanning was completed without complications, no adverse reactions to the contrast material occurred. The mean time between injury and neuropsychological testing was 110 days (SD 66). In all patients, perfusion CT scanning was completed without complications, no adverse reactions to the contrast material occurred.

Table 1. Patient characteristics.

Patient characteristics (N = 18)		
Mean age in years, mean (SD)		35.2 (14.3)
Male		13 (72%)
Traffic accidents		14 (78%)
GCS, mean (SD)		14.0 (0.5)
	15	2 (11%)
	14	14 (78%)
	13	2 (11%)
Duration PTA in hours, mean (SD)		10.7 (12)
Complaints#		14 (78%)
GOSE, mean (SD)		6.6 (0.9)
	8	3 (17%)
	7	5 (28%)
	6	9 (50%)
	5	1 (6%)
Return to work	Complete	7 (39%)
	Parttime	9 (50%)
	Lowerlevel	-
	Not working	2 (11.1%)

Abbreviations: GCS = Glasgow Coma Score, PTA = posttraumatic amnesia, GOSE = extended Glasgow Outcome Scale. Values are number (%) unless noted otherwise. #: number (%) of patients with two or more complaints.

Neuropsychological tests and cerebral perfusion

The mean score on the 15 Words test IR was 40.3 (SD 11.3), on the FEEST 45.9 (SD 6.3), on the Trailmaking test part B 81.0 (SD 34) and on the Zoo Map test 12.1 (SD 3.8). Five out of eighteen

patients (28%) had deficient scores on the 15 Words test, six performed abnormal on the FEEST (33%), five out of seventeen patients (29%) had abnormal scores on the Trailmaking test part B and four patients (24%) had deficient scores on the Zoo Map test. One patient had abnormal scores on all four tests, one patient had deficient scores on three tests, three patients had deficient scores on two tests and eight on one test. Five patients had no abnormal scores. Significant differences are summarised in Figure 1.

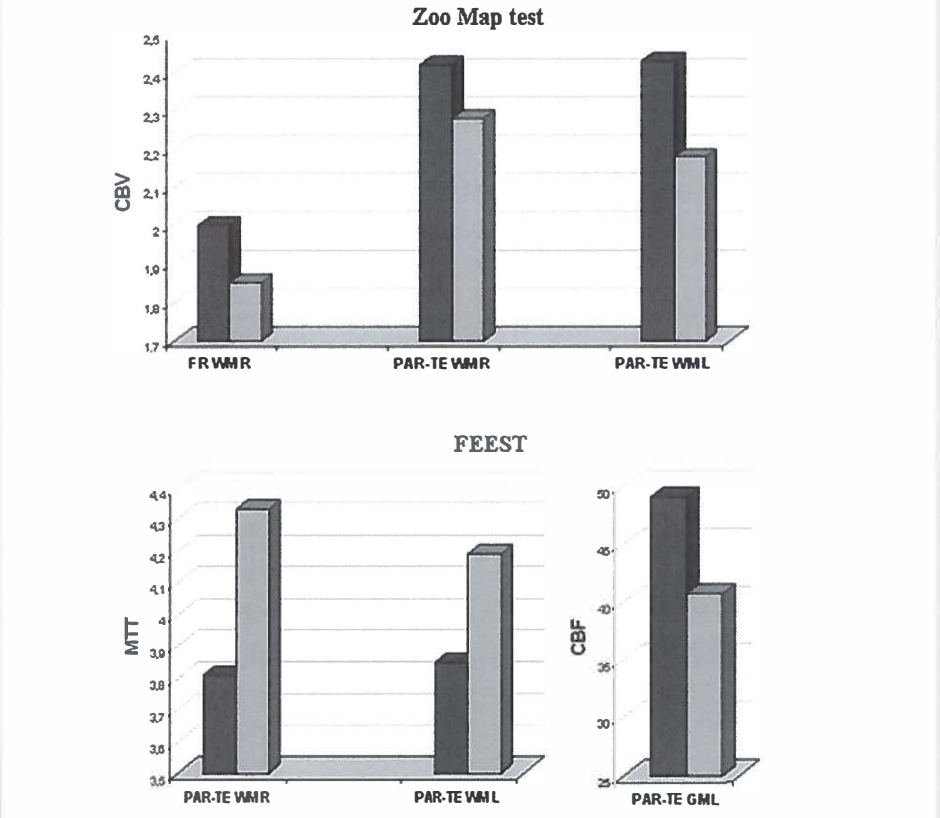

Figure 1. Cerebral perfusion in relation to neuropsychological tests.
Significant ($P < 0.05$) differences in cerebral blood volume (CBV), mean transit time (MTT) and cerebral blood flow (CBF) between those with normal (dark bars) and abnormal (light bars) neuropsychological test results on the Zoo Map test and the FEEST.
Abbreviations: FR = frontal, PAR-TE = parieto-temporal, WM = white matter, GM = grey matter, R = right hemisphere, L = left hemisphere.

There were significant ($P < 0.05$) differences in cerebral perfusion between those with normal and abnormal scores on the Zoo Map test and the FEEST. Patients with an abnormal score on the Zoo Map test had a significant lower CBV in the right frontal white matter (1.85 vs. 2.00 ml • 100 g^{-1}) and the right (2.28 vs. 2.42 ml • 100 g^{-1}) and left (2.18 vs. 2.43 ml • 100 g^{-1}) parieto-temporal white matter. Patients with an abnormal score on the FEEST had a significant higher MTT in the parieto-temporal white matter on both sides (right: 4.33 vs. 3.81 sec; left: 4.19 vs. 3.85 sec) and a significant lower CBF in the parieto-temporal grey matter on the left side (40.7 vs. 49.0 ml • 100 g^{-1} • min^{-1}).

No significant relation could be discerned between the dichotomised neuropsychological test data and the severity and number of complaints. In addition, there was no significant relation between the dichotomised neuropsychological tests and outcome according to the GOSE and RTW.

DISCUSSION

Mild TBI is a major public health issue. Between 80-90% of all traumatic brain injuries are considered mild, and of these, up to 20% is associated with persisting cognitive symptoms. [2,6,37] The pathophysiological base of these long-term sequelae after TBI is not fully understood. Multiple factors are proposed as contributors in generating and maintaining these symptoms. [3] The consistency and clustering of symptoms over time after mild TBI could point to cerebral dysfunction as the primary cause. [3,38] In addition, the fact that imaging studies mostly do not reveal structural abnormalities, suggest to determine eventual functional abnormalities. This is the first study that analysed acute cerebral perfusion in relation to neuropsychological testing at follow-up in mild TBI patients with a normal conventional CT. It revealed that mild TBI patients with impaired prefrontal regulated functions, i.e. executive functioning and social cognition assessed with neuropsychological tests during follow-up had significant different cerebral perfusion in the acute phase of trauma compared to those with normal neuropsychological tests. The question is whether these early changes in perfusion could provide a pathophysiological concept of long-term neuropsychological test results.

Cerebral hemodynamics in mild traumatic brain injury

In the acute phase of mild TBI, a small number of hemodynamic imaging studies have been performed before such as SPECT, [23-25] Xenon-CT [26] and perfusion CT. [27] These studies mostly revealed hypoperfusion in the frontal and temporal lobes, basal ganglia and thalami and to a lesser extend in the occipital lobes. Very recently, a SPECT study performed in the acute phase of mild TBI combined with a neuropsychological assessment during follow-up revealed that perfusion abnormalities were associated with an increased chance of long-standing memory deficits. [39] One of the major differences compared to the present study is that they included a relative large proportion (30%) of patients with abnormalities on the conventional CT. It is known that cognitive outcome is worse in those patients with abnormalities on conventional CT or MR imaging [40-43] and is correlated with its size and location. [44] Nevertheless, false negative rates were higher for the conventional CT than SPECT in predicting neuropsychological abnormalities. [39] Earlier, Jacobs and colleagues obtained similar results with SPECT in mild brain injured patients in the subacute and chronic phase but they use posttraumatic symptoms instead of standardised neuropsychological tests as an outcome measure. [45,46]

Cognition after mild traumatic brain injury

In the current study at least one in four patients showed deficient scores on several neuropsychological tests. When perfusion changes are related to neuropsychological test results, the issue has to be clarified whether specific tests and even specific anatomical regions are involved. Long-term cognitive deficits are described in mild TBI in a broad range of cognitive

domains with attention, memory, speed of information processing, verbal fluency and executive functions mostly affected. [14-19] Also in the present study, mild TBI patients revealed cognitive deficits regarding immediate memory (15 Words test), attention, speed (Trailmaking test part B), executive functions (Trailmaking test part B and Zoo Map test) and social cognition (FEEST). To our knowledge impairments of social cognition in mild TBI are described less frequently. Although a relation with severity of injury had been described, [47-49] most studies include more severely head injured patients or do not specifically address the mildly injured patients in studies containing patients with various severity of injury. A recent study by Spikman and colleagues on moderate and severe TBI revealed significant deficits in social cognition with the highest effect size for the emotion perception test, the FEEST. [34] Interestingly, the present study revealed a relation between cerebral perfusion in the frontal and parieto-temporal areas and neuropsychological test results encompassing executive functioning and social cognition. In particular, the FEEST and Zoo Map tests were found to be more sensitive suggests a role of prefrontal regulated functions. An explanation for the fact that no relation could be discerned between cerebral perfusion and the 15 Words Test and the Trailmaking test part B, could be that these tests offer more structure compared to the FEEST and Zoo Map tests, and hence are less dependent on prefrontal regulated functions. In addition, the finding that no relation with GOSE and RTW was present could be explained by the fact that the cognitive changes are often subtle and escape attention, although with specific outcome measures the long-term influence of these changes is related to RTW. [4]

Frontal lobes and network function

Impairment of executive functions and social cognition is related to frontal dysfunction. It is known that the prefrontal cortices in particular, play a key role in executive functioning [50-52] with involvement of other areas like the parietal lobes and cingulate gyrus as an executive network. [53] In addition, it is shown that social cognition tests are significantly related to an orbitofrontal lesion location. [34] One could speculate that hemodynamic processes in the acute phase of traumatic brain injury lead to alterations in the brain structure and functional networks, although no gross pathophysiology is visible on the conventional CT-scan. These changes could be related to diffuse axonal damage also present in mild TBI, as seen in pathological studies. [54-56] Diffuse tensor imaging (DTI) studies on mild head injured patients mainly revealed reduced fractional anisotropy [57-62] suggestive of axonal injury in wide spread white matter areas, mostly in the frontal areas, in normal appearing white matter on conventional structural imaging. [63] In another analysis we found a relation between perfusion CT imaging in the acute phase and DTI abnormalities during follow-up in mild TBI. [64] Hemodynamic alterations and white matter tracts abnormalities could be regarded as interrelated phenomena in the pathophysiology of TBI although the precise chronology of pathophysiological processes remains poorly understood. Consequently, if posttraumatic alterations in brain structure could influence long-term

functioning resulting in cognitive deficits other imaging techniques could provide additional information. For example, functional MRI (fMRI) studies in mild TBI have indicated that different patterns of activation after injury may be present. [37] In an fMRI study one month post injury, the patient group revealed significant different activation patterns on working memory tasks compared to controls, especially in the frontal and parietal regions. [65] Also, different post injury activity patterns on the longer term were found in athletes with mild TBI on working memory tasks, particularly in the prefrontal cortex. [66, 67] Even in the resting state, when a person is not performing a particular task, a decreased functional connectivity in the default-mode network, which includes the prefrontal cortex and posterior cingulate gyrus, was revealed. This altered functional connectivity in the subacute phase was normalised in the more chronic phase after injury. [68] To note, in our patient group deficits in particular tasks concerning executive functioning and social cognition were associated with a decreased cerebral perfusion in the frontal and parieto-temporal areas.

This is the first study that revealed a relation between acute cerebral perfusion and neuropsychological testing at follow-up in patients with mild TBI with a normal conventional CT, what could provide clues for the concept of acute versus chronic alterations in traumatic brain injury. However, some limitations of the study design have to be mentioned. The magnitude of the study group did not allow extensive analysis of outcome or comparison of individual cerebral perfusion with concerns group to differences. Furthermore, because of the small sample size, results have to be interpreted with caution. In addition, the presented group can be regarded as a subgroup of the mild TBI population, as these patients had complaints during follow-up. Nevertheless, we think that this is a relevant subanalysis regarding the pathophysiological mechanisms of suboptimal outcome in this patient category. Especially considering the fact that in patient care, cognitive complaints are often the presenting symptom in disturbed work resumption in this category of patients. Furthermore, pre-morbid factors could influence the present results, particularly regarding personality traits like coping strategy as the ability to adapt adequately to changing situations also depends on the integrity of prefrontal, executive brain functions. In further studies it would be interesting to compare acute perfusion disturbances with changes over time earlier after injury.

Concluding, a relation between cerebral perfusion changes in the acute phase of mild TBI and neuropsychological test abnormalities during follow-up encompassing executive functioning and social cognition provides challenging concepts for long-term impairment of mild TBI.

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Chapter

8

Integrated discussion and future perspectives

SUMMARY AND INTEGRATED DISCUSSION

In recent years advances in neuroimaging techniques have increased our comprehension of the relation between the severity of traumatic brain injury (TBI) and its outcome. These techniques have contributed to the knowledge of the pathophysiological processes in TBI, although the precise sequence of events in brain injury after trauma is not yet completely understood. Novel structural imaging techniques allow the visualisation of hemodynamic and metabolic changes in the brain. These techniques are extensively reviewed in **chapter 2**.

With regard to the sequence of events, TBI is classically divided in primary and secondary injury. Primary brain injury occurs at the moment of impact, with diffuse axonal injury (DAI) as the most important injury mechanism.[1-4] In pathological studies DAI may also be found in mild TBI, although its severity increases with the severity of the clinical condition as defined by the Glasgow Coma Score (GCS).[5-7] Primary brain injury also includes focal abnormalities such as parenchymal contusions and hematomas, as a result either of direct impact or of accelerated movement of the brain within the skull.[2,6] These primary induced injuries are best visualised by structural brain imaging methods, with the conventional non-contrast CT scan being regarded as the most appropriate diagnostic tool in acute clinical care. However, in 20% of the patients with mild to moderate TBI the initial non-contrast CT scan does not reveal any abnormalities whereas patients have residual complaints that interfere with resumption of work.[8] This implies that a non-contrast CT scan has a limited ability to detect structural and functional abnormalities. The main cause of secondary brain injury is ischemia, which may evolve in the hours after impact. Ischemia is more appropriately visualised with imaging methods that focus on cerebral metabolism and perfusion.

To examine the cerebral perfusion in the acute phase after mild TBI we performed perfusion CT imaging as outlined in **chapter 3** and **4**. Only a few earlier studies on cerebral perfusion in the acute phase of mild TBI were available, using single photon emission computed tomography (SPECT)[9-13] and Xenon-CT.[14] We found, with perfusion CT imaging, significant differences in cerebral perfusion between patients and healthy control subjects. Especially in the frontal and occipital grey matter significant decreases of cerebral blood flow (CBF) and cerebral blood volume (CBV) were measured in those patients with a GCS of 13 or 14. Previous studies also found hypoperfusion, predominantly in the frontal and temporal lobes and to a lesser extent in the occipital lobes,[9-11,13] but these studies measured global perfusion only and, hence, did not differentiate between white and grey matter areas. It is unclear whether these reductions in CBF represent true ischemia, reduced functional activity, disturbed autoregulation or neuronal damage. Research on focal ischemia caused by arterial occlusion revealed that neurological dysfunction occurs if CBF decreases below 18-20 ml • 100 g^{-1} • min^{-1}, while cell death occurs within minutes to hours if CBF falls to levels between 10-20 ml • 100 g^{-1} • min^{-1}.[15-17] These values are far below the values found in our study. Hence, regional ischemia after mild TBI is

highly unlikely. In patients with a GCS 15 we found an actual CBF increase. This could be a compensatory vasodilatation of intraparenchymal vessels as a result of autoregulatory mechanisms. [37,38] Most studies examining the value of CBF and CBV are performed in severe TBI patients, in whom high global CBF and CBV values are known to be associated with intact autoregulation and favourable outcome. [25,39] Sakas and colleagues also revealed cerebral hyperemia predominantly in those with mild TBI and found an association with favourable outcome. [40] The issue remains whether the demonstrated alterations in CBF can be related to changes in functional activity. From PET studies we know that in visual tasks perfusion in the occipital lobes increases up to 10%. [18] Thus, it could be hypothesised that altered arousal states like agitation due to posttraumatic amnesia (PTA) would lead to an elevated cerebral perfusion. Instead, patients who were scanned in our study during their period of PTA had a decrease in CBF in the frontal grey matter. Although we did not assess the arousal states of patients during scanning, TBI patients are mostly agitated and restless during their period of PTA. [19,20] This implies that the decrease in cerebral perfusion we found could be an underestimation of the actual cerebral perfusion as representative of neuronal functioning. For future studies, using imaging techniques to compare changes in perfusion with concurrent changes in cerebral metabolism might provide further insight in this topic.

Chapter 5 describes an elevation in serum of the neuronal marker Glial Fibrillary Acid Protein (GFAP) in mild TBI patients with abnormalities on non-contrast CT. In those with normal CT this biomarker often was not detectable. Abnormalities on follow-up MRI in those with elevated serum GFAP levels suggested a prognostic value. In an unpublished sub-analysis no relation was found between cerebral perfusion and GFAP. In previous studies on severe TBI, GFAP was higher in those with more severe brain injury, as defined by a lower GCS or structural imaging abnormalities. [21-23] In mild TBI we postulate that cerebral perfusion imaging is a better indicator of subtle traumatic cerebral derangements than serum GFAP analysis. Nevertheless, we recognize that neuronal damage as measured by serum GFAP can be indicative of structural pathophysiology in mild TBI. Multivariate analysis revealed that serum GFAP was not an independent outcome factor. Therefore, the relation between injury severity and ultimate outcome in mild TBI is more complex than solely defined by these serum biomarkers.

In chapter 6 and 7 the relation between acute phase perfusion CT imaging in mild TBI and subsequent diffusion tensor imaging (DTI) with neuropsychological testing in the chronic phase after injury is outlined. These chapters support the hypothesis that a decreased cerebral perfusion is related to structural damage and consequent long-term neuropsychological deficits in a subgroup of patients with mild TBI.

Chapter 6 describes a trend towards abnormalities on DTI during follow-up, 4-6 months after mild TBI. These structural alterations, predominantly in the frontal with matter, are associated with the perfusion CT parameter CBV as measured in the acute phase of injury. DTI provides a powerful noninvasive tool to study the brain architecture and has revolutionised the field of

white matter mapping. [24,25] Two parameters, fractional anisotropy (FA) and mean diffusivity (MD) are the most commonly reported DTI parameters. Elevated FA may reflect axonal swelling or cytotoxic oedema whereas decreased FA may indicate axonal degradation with excess water between tracts or in perivascular spaces. In our study we found a lowered FA and an elevated MD, reflecting axonal damage, predominantly in the frontal lobes. These alterations in FA and MD are in accordance with previous studies in the chronic phase of mild TBI. [26-29] Although our study findings failed to reach statistical significance in terms of differences between patients and healthy control subjects, they suggest long-term structural axonal damage in these mild TBI patients. Supportive of this view was the significant relation between these follow-up DTI abnormalities and perfusion CT parameters acquired in the acute phase. Thus, these two imaging methods may reflect a continuum of early and late pathophysiological processes in TBI. Ueda and colleagues demonstrated in rat models that axonal damage is associated with vascular abnormalities in the early stage after injury. They suggested that injury forces might also damage the perivascular neuronal network, thereby contributing to the hemodynamic abnormalities. [30] Hence, the observed white matter abnormalities on DTI in our mild TBI group might be secondary to early cerebral hemodynamic dysregulation, or be part of the same pathophysiological process in the acute phase, which would explain the relation between perfusion CT abnormalities in the acute phase and DT imaging abnormalities during follow-up.

Chapter 7 describes the relation between acute perfusion CT imaging and neuropsychological testing during follow-up. Mild TBI patients with impaired prefrontally regulated functions, i.e. executive functioning and social cognition as assessed by neuropsychological tests, had a significantly lower initial frontal and parieto-temporal perfusion in the first hours after trauma than those with normal neuropsychological tests. Impairment of executive functions and social cognition is related to frontal dysfunction.[38] It is known that the prefrontal cortices in particular, play a key role in executive functioning [31-33] with other areas like the parietal lobes and cingulate gyrus being part of an executive network. [34] These findings corroborate our hypothesis that hemodynamic processes in the acute phase of traumatic brain injury can cause permanent changes in the brain's structure and its functional networks, despite the fact that no gross pathophysiology is visible on a non-contrast CT scan on admission.

RESULTS IN FUTURE PERSPECTIVE

Our research contributes to understanding the pathophysiology in mild TBI and provides conceptual relations between simple mechanical damage, vasoregulatory and hemodynamic changes, and the complexities of late clinical outcome in these patients.

There is no consensus in the literature on neuropsychological deficits after mild TBI. Several small studies have shown that persistent cognitive impairment can be present in patients after mild TBI. [35-40] Impairments at long-term follow-up have been documented in all cognitive domains, [41] with most deficits involving attention and concentration, [38] memory, [40,42] speed of information processing, [42] verbal fluency, [38] and executive functions. [42,43] In our patients we also found deficits in memory, attention, speed, executive functions and social cognition. Conventional imaging often does not display explanatory structural brain damage in such patients. Therefore, the actual injury mechanism and its relation with outcome may be complex. For years, malingering was supposed to be an important factor in those mild TBI patients with suboptimal outcome, as the symptoms appeared inconsistent with the severity of injury and the lack of imaging abnormalities. [44] In recent years, novel imaging methods have generated supportive evidence for a causal relationship between imaging and residual symptoms or neuropsychological impairment in mild TBI. Such data came from hemodynamical, [11,13,45-47] diffusion tensor, [25-28,48-52] and functional [52-56] neuroimaging. Furthermore, the consistency and clustering of symptoms over time suggests that cerebral dysfunction is an underlying cause. [57,58] These advanced neuroimaging methods are promising in their potential to help understand the pathophysiological substrates of mild TBI. Moreover, they may have prognostic relevance. However, caution is warranted with interpretation of results, as most methods are in the early stages of clinical application.

Most studies on outcome in mild to moderate TBI relate persistent cognitive complaints to physical and structural features (e.g. mechanism of injury, extra-cranial injuries and CT-abnormalities). Specific premorbid patient characteristics may also be relevant. In particular illness perception and coping style may be decisive for the development of postconcussive complaints and they are related to unfavourable outcome. Some patients are better able to adapt to and thus cope with injury and its consequences than others. [59,60] A passive coping style might cause depression and anxiety, which in turn will lead to excessive focussing on somatic and mental symptoms. In TBI patients it was consistently found that the use of active coping strategies was related to a better outcome and better functioning. [61-64]

An important element of coping is the ability to regulate emotions and adapt responses to a distressing situation. This ability to adapt adequately to changing situations depends on the integrity of prefrontal brain functions. Therefore, when elucidating the prognostic factors in mild TBI, the relation of these premorbid factors with prefrontal network integrity has to be taken into account.

Based on our study findings interesting future directions can be delineated. It was consistently found that impairments in the frontal regions were related to outcome. It is well known that the prefrontal cortex plays a key role in the regulation of adaptive responses to changes in task demands and social demands. These adaptive responses in turn are modified by feelings of anxiety and depression. Therefore, in addition to imaging, personality traits and psychological status should be included in any predictive or explanatory model that attempts to specify the relation between mild TBI and subsequent late clinical outcome.

In our imaging studies we found a significant relation between DTI abnormalities during follow-up and perfusion CT parameters acquired in the acute phase. This suggests that these two imaging methods reflect the same evolving pathophysiological process. As the white matter integrity is related to the functional networks of the brain, it would be interesting to explore whether the findings of the present study are related to changes in brain connectivity as measured with functional MRI (fMRI). In particular we should focus on the prefrontal cortex, combining imaging with neuropsychological testing. With tests that specifically target frontal dysfunction it should become possible to detect subtle frontal impairments in social cognition that are relevant to daily functioning. In addition, follow-up scanning should be performed using simultaneously different advanced imaging modalities that focus on cerebral hemodynamics and brain connectivity. Such imaging studies will have to be combined with neuropsychological testing in different phases after injury, in order to increase our understanding of the pathophysiological mechanisms of mild TBI and provide additional outcome predictors. Given the long-term consequences for our patients, it is a major challenge to unravel this complex field of prognostic factors further and to predict which patients will develop persistent cognitive complaints.

In conclusion, this study has been designed to provide additional prognostic factors for patients who suffered from mild TBI, especially in those with normal conventional imaging, and to elucidate pathophysiologic processes. Changes in cerebral perfusion are found in the acute phase, even in those in whom no abnormalities can be detected on conventional CT imaging. These cerebral perfusion abnormalities are of significant prognostic value. A relation between acute cerebral perfusion abnormalities and DTI and neuropsychological testing during follow-up could be established, indicating a pathophysiological continuum between hemodynamic changes and axonal damage in mild TBI patients.

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Chapter

9

Nederlandse samenvatting

Traumatisch hersenletsel (THL) is één van de meest voorkomende neurologische aandoeningen en één van de belangrijkste oorzaken van invaliditeit en overlijden.
De meerderheid (80-90%) van de patiënten krijgt een licht THL, wat gekenmerkt wordt door een Glasgow Coma Score (GCS) van 13 tot 15 en met tenminste een periode van bewustzijnsverlies of amnesie. De meeste van deze patiënten herstellen binnen weken tot maanden na het ongeval, echter een subgroep blijft klachten houden welke interfereren met hervatting van werk en sociale activiteiten. Deze symptomen hebben niet alleen persoonlijke maar ook socio-economische consequenties aangezien het vaak jonge mensen betreft die zich midden in het werkproces bevinden. Het is van groot belang om in een vroeg stadium die patiënten te kunnen identificeren die een grotere kans hebben op suboptimale uitkomst, zodat vroegtijdige begeleiding en revalidatie gestart kan worden. Eén van de eerste en meeste gebruikte beeldvormende technieken in de acute fase van THL is de conventionele CT scan. Deze is geschikt voor het aantonen van bloedingen, parenchymateus letsel en fracturen. Het is de meest relevante beeldvormende techniek voor toepassing in de acute fase van het THL om lesies te identificeren die in aanmerking komen voor neurochirurgische interventie. De sensitiviteit voor het aantonen van afwijkingen in de acute fase van THL bedraagt 63-75%. Echter, 20% van de patiënten met licht tot matig THL zonder afwijkingen op de conventionele CT scan ervaart problemen met werkhervatting. De precieze pathofysiologische mechanismen van THL zijn nog niet goed opgehelderd. Ontwikkelingen op het gebied van cerebrale beeldvorming kunnen leiden tot meer inzicht in deze mechanismen, de sensitiviteit voor het detecteren van afwijkingen doen toenemen en betere prognostische parameters opleveren.
De perfusie CT is een recent ontwikkelde beeldvormende techniek die gebruik maakt van de cerebrale hemodynamiek van intraveneus toegediende contrastvloeistof. Het is goed toepasbaar in de acute setting waarbij de cerebrale perfusie geobjectiveerd kan worden in combinatie met de conventionele CT scan.
De doelstelling van dit proefschrift was om meer inzicht te verkrijgen in de pathofysiologische mechanismen bij licht THL waardoor in een vroege fase direct na het ongeval betere prognostische parameters verkregen konden worden. Tevens werden de bevindingen van de perfusie CT vergeleken met de uitkomsten van neuropsychologische tests en diffusion tensor imaging (DTI) studies op lange termijn bij deze patiëntengroep.
In **hoofdstuk 2** wordt een uitgebreid overzicht weergegeven van de verschillende beeldvormende technieken en hun prognostische waarde bij patiënten met licht tot matig THL. Hoewel er voor de groep met ernstig THL veel literatuur beschikbaar is over prognostische factoren en beeldvorming in het bijzonder, is er minder bekend over licht THL ondanks het feit dat de meeste patiënten tot deze categorie van THL behoren. Dit overzichtsartikel richtte zich op structurele, hemodynamische en functionele beeldvormende technieken. De indicaties voor de toepassing van conventionele CT en MRI scan werden beschreven en de waarde van de verschillende MRI sequenties toegelicht. Wat betreft de hemodynamische en functionele beeldvorming werden

de toepassing van single photon emission computed tomography (SPECT), perfusie MRI, perfusie CT, positron emissie tomografie (PET), magnetische resonantie spectroscopie (MRS), functionele MRI en magnetoencephalografie (MEG) besproken. De voordelen en beperkingen van deze verschillende beeldvormende technieken werden bediscussieerd, in het bijzonder ten aanzien van de prognostische kwaliteiten en het vermogen om hersenschade te identificeren.

In **hoofdstuk 3** worden de resultaten beschreven van een prospectief gerandomiseerde studie naar de diagnostische en prognostische waarde van de perfusie CT in de acute fase van licht THL. De cerebrale perfusie van deze patiëntengroep werd vergeleken met een groep gezonde vrijwilligers. Dit onderzoek heeft laten zien dat er significante verschillen bestaan in de cerebrale perfusie tussen patiënten in de acute fase na licht THL en gezonde vrijwilligers. Met name in de frontale en occipitale grijze stof werd een lagere cerebrale bloedstroom en bloedvolume gezien. Tevens werd aangetoond dat een verminderde cerebrale bloedstroom en bloedvolume in de frontale gebieden van voorspellende waarde zijn voor een slechtere uitkomst volgens de extended Glasgow Outcome Scale (GOSE).

In **hoofdstuk 4** worden patiënten beschreven die een perfusie CT scan kregen gedurende hun periode van posttraumatische amnesie (PTA). Het bleek dat deze patiënten een significant lagere cerebrale bloedstroom in de frontale grijze stof en de nucleus caudatus hadden in vergelijking met patiënten die na hun periode van PTA werden gescand. Ook was een langere duur van PTA significant geassocieerd met een lagere cerebrale bloedstroom in de frontale grijze stof. De lagere cerebrale perfusie in corticale-, en subcorticale gebieden bij patiënten in PTA suggereert een tijdelijke neuronale dysfunctie. De mogelijke hieraan gerelateerde pathofysiologische mechanismen van PTA werden uitgebreid besproken.

In **hoofdstuk 5** is gekeken naar de prognostische waarde van de neuronale marker Glial Fibrillary Acid Protein (GFAP), welke in de acute fase na het trauma werd afgenomen. Tevens werd er gekeken naar de relatie tussen GFAP en eventuele cerebrale afwijkingen op CT en MRI. Het bleek dat de concentratie van GFAP verhoogd is bij die patiënten die afwijkingen hebben op de conventionele CT scan, terwijl de GFAP vaak niet aantoonbaar was bij patiënten met een normale conventionele CT scan. Ook bij patiënten die aanwijzingen hadden voor diffuus axonale schade op de follow-up MRI scan, bleek de GFAP verhoogd. In een niet-gepubliceerde subanalyse kon geen relatie aangetoond kon worden tussen de cerebrale perfusie en GFAP. Verder is vastgesteld dat GFAP significant hoger was bij patiënten met een suboptimale werkhervatting, echter in een multivariate regressie analyse bleek GFAP geen significante voorspeller voor de uitkomst te zijn.

In **hoofdstuk 6** is gekeken naar de relatie tussen perfusie CT bevindingen in de acute fase van licht THL en DTI bevindingen op lange termijn, met als doel om mogelijke pathofysiologische processen te verhelderen. DTI is een MRI sequentie die gevoelig is om axonale schade te detecteren. Uit dit onderzoek bleek dat er bij patiënten met licht THL verschillen zijn in DTI parameters in vergelijking met gezonde vrijwilligers, waarbij er significante correlaties bestaan

tussen cerebrale perfusie CT bevindingen in de acute fase na het ongeval en de DTI bevindingen op lange termijn. Deze relatie met de perfusie CT afwijkingen in de acute fase van het letsel is bediscussieerd als een pathofysiologisch continuüm, waarbij gepostuleerd zou kunnen worden dat perineurale capillairen in de acute fase van het hersenletsel beschadigd raken met als gevolg cerebrale perfusie stoornissen wat zou kunnen leiden tot axonale schade en derhalve afwijkingen op de DTI, ook op lange termijn.

In **hoofdstuk 7** wordt de relatie tussen de perfusie CT bevindingen in de acute fase van het ongeval en de neuropsychologische tests op lange termijn onderzocht. De resultaten lieten zien dat patiënten na licht THL cognitieve stoornissen kunnen hebben op het gebied van executief functioneren en sociale cognitie. Afwijkende scores voor deze pre-frontaal gereguleerde cognitieve functies gedurende de follow-up bleken significant te correleren met een lagere cerebrale perfusie in de frontale en parieto-temporale gebieden in de acute fase van het ongeval. De gegevens uit hoofdstuk 6 en 7 dragen beide bij aan de discussie omtrent de onderliggende pathofysiologische mechanismen als origine van een suboptimale uitkomst bij patiënten met licht THL.

Concluderend, dit onderzoek is opgezet om betere prognostische factoren te vinden voor patiënten met licht THL en, in het bijzonder, voor die patiënten met normale bevindingen op de conventionele CT scan bij opname. Daarnaast heeft dit onderzoek handvaten willen bieden ten aanzien van het begrip van de onderliggende pathofysiologische mechanismen van licht THL. Ten eerste is gebleken dat er bij patiënten met een licht THL en een normale conventionele CT scan cerebrale perfusie stoornissen aanwezig zijn in de acute fase van het ongeval. Ten tweede bleken deze cerebrale perfusie stoornissen van prognostisch belang te zijn. En ten slotte, zijn er relaties gevonden tussen deze perfusie CT afwijkingen in de acute fase en neuropsychologische en DTI afwijkingen op lange termijn, wat een pathofysiologisch continuüm suggereert.

Chapter

10

Appendices

APPENDIX I

Glasgow Coma Score (GCS)

Eye opening	
Spontaneous	4
To loud voice	3
To pain	2
None	1
Best motor response	
Obeys	6
Localizes	5
Withdraws	4
Abnormal flexion posturing	3
Extension posturing	2
None	1
Verbal response	
Oriented	5
Confused, disoriented	4
Inappropriate words	3
Incomprehensive sounds	2
None	1
Sum score	**3-15**

APPENDIX II

Posttraumatic Amnesia Questionnaire

Patients name _____

Date of injury _____

Date of PTA assessment _____ _____ _____ _____

	morning	afternoon	morning	afternoon
	day 1	day2	day3	day 4
Personal data				
1. Name your birthday	-	-	-	-
2. What is the year of your birth?	-	-	-	-
Orientation in place				
3. What kind of building are you in now?	-	-	-	-
4. What place you are now?	-	-	-	-
5. Name reason of admittance	-	-	-	-
Orientation in time				
6. Name present year	-	-	-	-
7. Name present month	-	-	-	-
8. Name present day	-	-	-	-
9. Name present time	-	-	-	-
Memory of daily activities				
10. What did you eat for breakfast?	-	-	-	-
11. Name recent visitors or an activity you did this morning/afternoon	-	-	-	-
12. Do you remember my name?	-	-	-	-
	_____ +	_____ +	_____ +	_____ +
Sumscore	-	-	-	-

APPENDIX III

OUTCOME SCORES

Extended Glasgow Outcome Scale (GOSE)

Good recovery	
no impairments	8
minor physical or mental deficits not interfering with return to work	7
Moderate Disability	
return to previous work with some adjustments	6
return to work at lower level of performance	5
Severe Disability	
for some activities dependent on others	4
completely dependent on others	3
Vegetative State	2
Death	1

Return to work (RTW) scoring form

previous work or study resumed	0
previous work or study resumed, but with lower demands or part-time	1
previous work or study not resumed, different work on a lower level	2
not working	3

Appendix IV

Cerebral perfusion CT in healthy volunteers: gender effects

ABSTRACT

The objectives were to obtain normal values in healthy volunteers with cerebral perfusion imaging and estimate gender effects on cerebral perfusion.

A total of 25 healthy control subjects underwent perfusion computed tomography (CT) imaging. Normal values were obtained for regions in the white and cortical grey matter. The cerebral blood flow (CBF) in the frontal cortical grey matter was significantly higher in females (48.8 ml • 100 g^{-1} • min^{-1} (SD 4.7)) compared to males (43.6 ml • 100 g^{-1} • min^{-1} (SD 5.3), P = 0.019). This gender differences are compared with findings from other imaging studies.

In perfusion CT, an imaging modality of increasing significance in research and clinical realms, gender should be used as covariates in statistical analyses.

INTRODUCTION

Perfusion computed tomography (CT) is a relatively new imaging technique with increasing applicability in several patient categories. After first being used in stroke patients, [1,2] this technique is increasingly applied in patients with subarachnoid hemorrhage [3] and traumatic brain injury (TBI). [4,5] In TBI, CT is mandatory in the emergency setting and can be easily combined with perfusion CT imaging. With the use of a relatively new diagnostic imaging method one should be aware of possible confounding effects on the data. Gender and age related influences in other imaging modalities are reported [6-8] in addition to neuropsychological correlates of gender differences. [6] With the use of a new imaging technique one should again verify these aforementioned effects as other imaging methods may rely on different principles with their specific side effects and systematic errors.

Most perfusion CT studies have derived normal values from patient data by comparison of the nonaffected hemisphere (in stroke patients) or regarding the values of patients with good outcome as normal (in TBI). So far, no study obtained perfusion CT data in healthy adult volunteers.

The purpose of our study was twofold. First, to obtain cerebral perfusion values in healthy volunteers with perfusion CT imaging. Second, to estimate gender effects on cerebral perfusion.

METHODS

Subjects

Twenty-five healthy subjects were enrolled in the study comprising 10 males and 15 females, with a mean age of 37.0 years (SD 12.43), and an age range spanning five decades. There was no significant difference (P = 0.95) in mean age between males en females (36.8 years (SD 11.1) vs. 37.1 years (SD 13.6), respectively). None of the subjects had a history of neurological diseases, psychiatric disorders, diabetes, nephropathy, iodium allergy, alcohol or drug abuse. All subjects gave their written informed consent. This group of healthy subjects was previous described in a prospective study regarding mild TBI, although quantitative values and intragroup analyses were not published before. [5] This study was approved by the Medical Ethical Committee (METC) of the University Medical Center Groningen.

Imaging

The CT scans were made on a Siemens Somatom Sensation 64-slice CT scanner (Siemens Medical Systems, Erlangen, Germany). Asymptomatic cerebral pathophysiology was excluded with a standard non-contrast CT of the brain. Before the perfusion CT scans were performed asymptomatic stenoses of the extracranial cervical arteries were excluded with color Doppler ultrasound examinations (Sonoline Antares Siemens Medical Systems, Erlangen, Germany).
In perfusion CT imaging, with a detector collimination of 24 x 1.2 mm, two adjacent 14.4 mm thick slabs were positioned at the level of the thalami, basal ganglia and third ventricle and at the level of the centrum semiovale and the lateral ventricles. Forty ml of a non-ionic iodinated contrast agent (Visipaque 270 mg/ml) was power-injected at a rate of 5 ml/s, followed by a 20-ml saline chase. After 5s delay, the scan was initiated with the following parameters: 80 kV, 100 mAs, and a rotation per 1 sec for a duration of 46 s. Post-processing was performed by an experienced neuroradiologist (L.R.) using TeraRecon perfusion software (TeraRecon Inc., San Mateo, CA). A Gamma variate fitting curve was applied. The deconvolution algorithm produced two sets of colored parameter maps for cerebral blood flow (CBF), mean transit time (MTT) and cerebral blood volume (CBV). By using a saved preset of regions of interest (ROIs), which could be manually adjusted, quantitative values for CBF, MTT and CBV were generated in the frontal, temporal and occipital white and grey matter on two slabs (Figure 1).

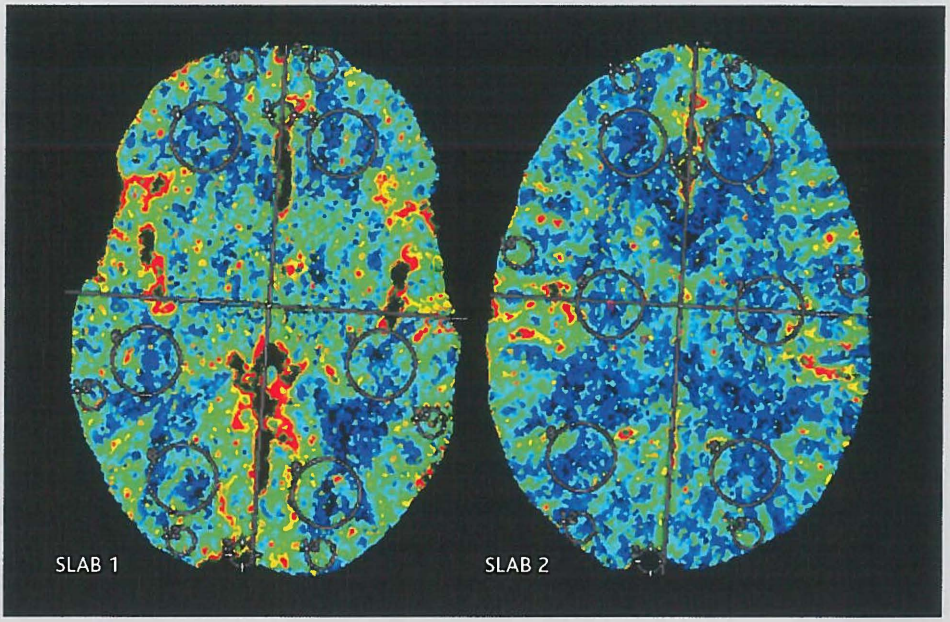

Figure 1. Two slabs with regions of interest (ROIs).
In each slab six ROIs were placed in the white matter and six ROIs were placed in the cortical grey matter. Slab 1 is lower slab; slab 2 is the upper slab.

Statistical analysis

All statistical analyses were done using SPSS (Statistical Package for the Social Sciences) version 16.0 (SPSS, Chicago, IL). Perfusion data from the two slabs were averaged. Paired t-test analyses, or if a variable was not normally distributed Wilcoxon signed rank tests, were used to compare white and grey matter areas and right and left hemisphere for CBF, MTT and CBV. Analysis of variance (ANOVA) was used for calculating the relationship between cerebral perfusion and gender. When gender or age related influences on cerebral perfusion were measured, correction for age-, and gender were made respectively by using them as covariates in the analysis (ANCOVA). These analyses were stratified by the six anatomical regions in the frontal, parieto-temporal and occipital grey and white matter. Statistical significance was defined as P-value < 0.05.

RESULTS

Cerebral perfusion values

In frontal, parieto-temporal and occipital white- and grey matter normal values were obtained for CBF, MTT and CBV. The results are displayed in Table 1.

The CBF, MTT and CBV differed significantly between white and grey matter areas. The CBF was 1.35 times higher in the cortical grey matter ($P < 0.001$), for the CBV this ratio was 1.36 ($P < 0.001$). The MTT was significant lower in de cortical grey matter (ratio 0.94, $P < 0.001$). No significant differences were present in CBF, MTT and CBV between the right and left hemisphere, stratified for white and grey matter areas. No significant relation was found between age and CBF.

Table 1. Normal values with perfusion computed tomography (CT) imaging.

	Areas	CBF (ml• 100 g^{-1} • min^{-1})	MTT (sec)	CBV (ml • 100 g^{-1})
	Global	**33.9± 4.1**	**4.5± 0.6**	**2.2± 0.3**
WM	Frontal	31.0±4.7	4.4±0.7	2.0±0.3
	Temporo-parietal	37.0 ± 5.1	4.3±0.6	2.4±0.2
	Occipital	33.6±3.9	4.7±0.7	2.3±0.3
	Global	**45.5 ± 4.3**	**4.3±0.6**	**3.1 ± 0.3**
GM	Frontal	46.7±5.5	4.1 ±0.7	3.0±0.4
	Temporo-parietal	48.0±5.6	4.0± 0.7	3.2±0.3
	Occipital	41.7± 5.1	4.8±0.8	3.1 ±0.4

Normal values for cerebral blood flow (CBF), mean transit time (MTT) and cerebral blood volume (CBV) in white matter (WM) and grey matter (GM) in different cerebral regions (see Figure 1).
Data represent mean ± SD.

Gender influences

When examining global CBF, MTT and CBV no significant gender differences were found. However, when examining separately white and grey matter differences (Table 2), the CBF in females was significantly ($P = 0.019$) higher (48.8 ml • 100 g $^{-1}$ • min $^{-1}$ (SD 4.7)) in the frontal cortical grey matter than in males (43.6 ml • 100 g $^{-1}$ • min $^{-1}$ (SD 5.3)), corrected for age influences. Furthermore, a nearly significant difference ($P = 0.054$) in CBF was found in the temporo-parietal white matter between females (38.6 ml • 100 g $^{-1}$ • min $^{-1}$ (SD 5.5)) and males (34.5 ml • 100 g $^{-1}$ • min $^{-1}$ (SD 3.3)).

Table 2. Differences in cerebral perfusion between males and females.

	Areas	CBF (ml • 100 g^{-1} • min^{-1})		MTT (sec)		CBV (ml • 100 g^{-1})	
	Gender	M	F	M	F	M	F
WM	Frontal	30.7±5.7	31.2±4.1	4.6±0.9	4.3±0.6	2.1±0.3	2.0±0.3
	Temporo-parietal	34.5±3.3	38.6±5.5	4.4±0.7	4.2±0.5	2.4±0.2	2.4±0.3
	Occipital	33.0±3.4	34.0±4.3	4.8±0.8	4.6±0.6	2.4±0.3	2.3±0.3
GM	Frontal	43.6±5.3	48.8±4.7*	4.3±0.8	3.9±0.5	3.0±0.4	3.0±0.4
	Temporo-parietal	46.6±4.1	48.9±6.4	4.3±0.8	3.8±0.6	3.3±0.3	3.1±0.4
	Occipital	40.7±4.2	42.4±5.6	5.1±0.8	4.7±0.7	3.2±0.3	3.0±0.4

Values for cerebral blood flow (CBF), mean transit time (MTT) and cerebral blood volume (CBV) in white matter (WM) and grey matter (GM) in different cerebral regions for males (M) and females (F). Data represent mean ± SD.
* = $P < 0.05$.

10

Comparison with other imaging techniques

Perfusion values obtained with perfusion CT and other imaging techniques are displayed in Table 3. It is noted that even within the same imaging technique various values regarding white and grey matter CBF are present. Our data is comparable to those of Pantano and colleagues. [9]

Table 3. Literature overview.

References	M/F	Age (yrs)	Imaging Modality	CBF (ml • 100 g^{-1} • min^{-1})		MTT (sec)		CBV (ml • 100 g^{-1})	
				GM	WM	GM	WM	GM	WM
Leenders et al [8]	18/16	22-82	PET	52.1±11	22.1±4.9			4.6±1.0	2.7±0.6
Pantano et al [9]	19/8	19-76	PET	47.7±10.9	24.7±5.3				
Koyama et al [10]	10/0	20-32	PET	64.1±7.0	24.2±3.7				
Koyama et al [10]	7/3	34-63	HMPAOSPECT	61.5±5.6	43.0±4.8				
Koyama et al [10]	8/2	36-62	ECDSPECT	59.3±6.9	38.9±5.8				
Parkes et al [11]	15/19	20-67	ASL MRI	M: 58±13	M: 23±3				
				F: 68±10	F: 25±5				
Helenius et al [12]	40/40	22-85	DSC MRI	94.2±23.0	19.6±5.8	3.0±0.6	4.3±0.7	4.6±1.0	1.3±0.4
Vonken et al [13]	N = 41	40-86	DSC MRI	68.7±21.2	35.8±12.7	6.4±1.8	6.9±2.3	6.8±1.0	3.8±1.0
Koshimoto et al [14]	8/11	25-73	DSC MRI	37.3±8.4		6.8±1.3	7.8±1.1	4.1±0.8	2.9±0.4
Schreiber et al [15]	N = 11	24-35	DSC MRI	67.1±16.3	23.7±4.9	4.7±0.8	5.4±1.1	5.3±0.9	2.5±0.4
Present study	**10/15**	**18-59**	**PCT**	**45.5±4.3**	**33.9±4.1**	**4.3±0.6**	**4.5±0.6**	**3.1±0.3**	**2.2±0.3**

Overview of cerebral perfusion values in the literature obtained with different imaging techniques compared with the present perfusion CT study
Abbreviations: CBF = cerebral blood flow, MTT = mean transit time, CBV = cerebral blood volume, M = male, F = female, GM = grey matter, WM = white matter, PET= positron emission tomography, SPECT = single photon emission computed tomography, HMPAO = hexamethylpropylene amine oxime, ECD = ethyl cysteinate dimer, ASL = arterial spin labelling, DSC = dynamic susceptability contrast, PCT = perfusion computed tomography.

DISCUSSION

In this study cerebral perfusion values were obtained in healthy volunteers and the contribution of gender on the cerebral perfusion with perfusion CT imaging was evaluated. The most important finding was a significant higher CBF in de frontal grey matter in women compared to men, underlining the importance to take gender into account when using a new imaging technique in a patient population.

Normal values

When comparing left and right cerebral hemispheres no significant differences were found. In contrast to other studies, no significant age-related differences regarding CBF were found. The reason that we could not discern a relation between age and CBF is probably related to the underrepresentation of the very elderly as the maximum age in our group was 59 years. [16] A study by Chen and colleagues supports this assumption as only older aged healthy volunteers (age ≥ 60) had a significantly lower mean CBF across the cortical grey matter. [17]

The mean perfusion values for CBF, MTT and CBV were compared with values from the literature. Comparisons between different imaging techniques, however, should be carried out carefully because different techniques are based on different theories and use their own tracers or contrast agents with different properties and kinetics. For instance in most dynamic susceptibility contrast magnetic resonance imaging (DSC-MRI) studies the CBF is higher compared to results of positron emission tomography (PET), single-photon emission computed tomography (SPECT) studies and our perfusion CT results, probably because DSC-MRI is sensitive for the total blood compartment in the measured tissue, including that of the arterioles and venules. [13] Nevertheless, the acquisition of normal values for an imaging technique enables comparison of perfusion parameters obtained with other perfusion CT studies in various patient populations.

Gender

We observed a significant higher CBF in women compared to men, predominantly in the frontal cortical grey matter. To provide an explanation for this perfusion difference one can hypothesise whether structural or functional mechanisms account for this finding. First, structural anatomical gender differences like a larger frontal grey matter volume can result in a higher local perfusion in women. Second, it could be explained by functional gender differences as variance in neuropsychological abilities between men and women related to frontal lobe function are well known. These two hypothesises are in fact related to each other.

According to a majority of studies women exhibit higher grey matter volumes compared to men. [6,7,18,19] However, there is little agreement in the literature on topography of sex differences in regional volumes. Goldstein and colleagues estimated that this larger proportion of cortical volume in women is predominantly located in the precentral gyrus, fronto-orbital cortex, superior

frontal and lingual gyri. Nevertheless, men had larger volumes in frontomedial cortex. [18] Schlaepfer and colleagues assessed that women had a larger dorsolateral prefrontal cortex and superior temporal gyrus compared to men. While in the more visiospatially related cortical regions this was not the case. [20]

Overall, these anatomical gender differences do, although not uniformly, support the hypothesis that women have a larger area of frontal grey matter and hence a higher frontal perfusion.

When evaluating gender related differences in cerebral function, perfusion variance can be related to changes in cerebral hemodynamics and metabolism, which mostly is studied by PET imaging. In a PET study on cerebral glucose metabolism by Miura and colleagues no gender differences in whole brain or regional cerebral glucose uptake were found [21] whereas Kawachi revealed focal differences in cerebral glucose metabolism using statistical parametric mapping. Males showed a significant higher glucose metabolism in the right insula, middle temporal gyrus and medial frontal lobe, while females had a significant higher glucose metabolism in the hypothalamus. [22]

A SPECT combined with three-dimensional MRI revealed a slightly higher temporal grey matter concentration in women while men showed a higher grey matter concentration in the upper cerebellar hemispheres. Comparison of functional data with the structural data revealed no significant mismatches between men and women [19,23] but after correction of gender-related CBF differences for partial volumes, women showed higher perfusion in left inferior frontal gyrus than men. [24] Also Ragland and colleagues estimated gender differences in regional CBF with greater bilateral CBF in midtemporal brain regions in women. [25] Esposito and colleagues revealed, combining neuropsychological tasks with a ^{15}O-water PET study in healthy volunteers, a significant higher global CBF in women while performing frontal lobe tasks. [26] Interestingly, no significant performance differences for the neuropsychological tests between men and women were found. Other studies reveal that in cognitive tests women perform better on tasks for verbal memory and verbal fluency than men. [25] Furthermore, women perform better on switching tasks, which are related to fronto-executive functioning. [27,28]

Summarised, there is a trend regarding gender differences in cerebral functioning with higher CBF in the frontal lobes in women. Therefore, we do think that these aforementioned cognitive gender differences, which imply a better verbal and executive performance in women, could help explain the higher frontal cortical CBF in women in our study.

There are some limitations in this study that have to be mentioned. First, iodinated contrast medium has vasomotor effects and, hence, it could influence cerebral perfusion by itself. Therefore, it is necessary to compare results obtained with perfusion CT within subjects or with normal values obtained with perfusion CT and not with functional imaging studies based on other techniques and hence use different markers or contrast agents. Second, the limited sample size of our study has to be mentioned. However, studies in normal volunteers vary from 10 to 80 participants in which there is an inverse relation between sample size and and the application

of contrast material and X-ray exposure. Furthermore, our results were significant in line with results of other imaging studies of comparable magnitude.

To conclude, in healthy volunteers cerebral perfusion values were obtained with perfusion CT imaging for CBF, MTT and CBV. Gender related differences for CBF were observed. Therefore, we suggest that gender should be as a covariate in statistical analyses, because of its estimated effect on cerebral perfusion with application of the perfusion CT.

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Dankwoord

Curriculum vitae

List of publications

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CURRICULUM VITAE

Zwany Metting werd op 21 juli 1975 geboren te Groningen. In 1995 behaalde zij haar Atheneum diploma aan de Aletta Jacobs Scholengemeenschap te Hoogezand. Na uitloting voor de studie Geneeskunde volgde zij het propedeuse jaar Farmacie waarna ze overstapte naar Pedagogische Wetenschappen aan de Rijksuniversiteit Groningen alwaar zij in 1997 begon met de bovenbouwstudie Bewegingswetenschappen. In 1998 werd zij ingeloot voor de studie Geneeskunde aan de Rijksuniversiteit Groningen. In 2003 groeide haar interesse voor de neurologie en de kinderneurologie in het bijzonder en verrichtte zij onderzoek naar het kind met het subdurale hematoom (Prof. dr. O.F. Brouwer). De co-schappen werden gedaan in het Universitair Medisch Centrum Groningen en in de laatste fase van haar studie deed zij haar keuze-coschap op de afdeling neurologie. Ze behaalde in december 2004 haar artsexamen. In januari 2005 begon ze met haar opleiding tot neuroloog in het Universitair Medisch Centrum Groningen (opleiders prof. dr. J.H.A. De Keyser opgevolgd door prof. dr. H.P.H. Kremer). Deze opleiding combineerde zij met wetenschappelijk onderzoek in de vorm van een AGIKO constructie. De registratie als neuroloog vond plaats op 1 juli 2012. Op dit moment is zij werkzaam als fellow kinderneurologie op de afdeling kindergeneeskunde in het Martini Ziekenhuis te Groningen.

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Metting Z, Rödiger LA, De Keyser J, Naalt van der J. Structural and functional neuroimaging in mild-to-moderate head injury. Lancet Neurol 2007;6:699-710.

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